

*Translated from the Danish*

by

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*nee Claessen*

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# HYPOSPADIAS

WITH SPECIAL REFERENCE  
TO ÆTIOLOGY



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MUNKSGAARD

1933

DENNE AFHANDLING  
ER AF DET LÆGEVIDENSKABELIGE  
FAKULTET VED KØBENHAVNS UNIVERSITET ANTAGET  
TIL OFFENTLIG AT FORSVARES FOR DEN  
MEDICINSKE DOKTORGRAD

*København den 19 februar 1933*

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## PREFACE

The studies to be reported were commenced 1916 during my time of service in Surgical Clinic C of Rigshospitalet Copenhagen at the initiative of Professor *E. Dahl Iversen* M D. The essential part of the material however was collected while I was assistant to the University Institute of Human Genetics. To its chief Professor *Tage Kemp* M D and to Professor *F. Dahl Iversen* M D I owe a debt of gratitude for advice guidance and practical assistance rendered in the course of my studies.

The patients were derived in part from lying in Department B of Rigshospitalet in part from the following surgical departments University Clinics C and D of Rigshospitalet Departments I and V of the Copenhagen City Hospital Departments A and D of Bispebjerg Hospital the Aarhus University Clinic and the Aarhus County Hospital. I am indebted to Professor *Ibbe Brandstrup* M D Professor *F. Dahl Iversen* M D Professor *S. Kjergaard* M D Professor *Otto Mikkelsen* M D *Torben Knudtzon* M D Professor *Jens Foged* M D Professor *H. Retten Abrahamsen* M D Professor *V. Alkjer* M D and *J. Fabricius Møller* M D for having kindly permitted me to use the case records from their departments.

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Copenhagen, February 1954

*Hans Rahbek Sorensen*

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## INTRODUCTION

Hypospadias is a congenital defect which in severe cases may be a cause of great concern to the patients and their parents. The worry is not only due to the difficulty of micturition and the fear that the patient will be unable to lead a normal sexual life, but also to the widespread idea that there is something inferior about malformed genitals. This inferiority complex is often fed by the attempts of well-meaning parents to hide their child's defect.

Surgical correction has been connected with great difficulties, and even though the results are constantly improving, a severe case may require several operations.

The deformity is generally considered inheritable by Mendelian dominance perhaps with failing manifestation. This opinion is based on the case reports of more or less thoroughly studied families. Therefore, the mode of inheritance has not yet been definitely established.

### *Object of the Present Study*

This study was designed mainly to elucidate the heredity by a proband study including an investigation of the genetic relation between the various degrees of this deformity. This involved a determination of the incidence of the defect and of the fertility among the patients. In the course of the study moreover, it proved necessary to look for aetiological factors other than genetic ones.

In addition it was endeavoured to elucidate the relation of hypospadias to Goldschmidt's intersexuality theory by statistical genealogical methods.

This volume does not by any means pretend to be a monograph on



*hypospadias. Many aspects are not considered. An analysis of the therapeutic results might have been desirable but the material was not suitable. In part it is derived from a period during which great advances have taken place within plastic surgery and in part the surgical methods used were so varied that an evaluation of the results would have been difficult. On the other hand the material may serve in evaluating the operative criteria.*

## Chapter I

### MORPHOLOGY

Hypospadias is generally defined as the congenital opening of the urethra on the under side of the penis (*Kaufmann* (1886), *Frangenheim* (1928), *Schneider* (1928), *Johnson* (1929), *Jeanbrau* (1937), *McGree* (1940), *Goldstein* (1946))

The abnormal orifice may be anywhere between the glans and the perineum so that the deformity may be more or less pronounced. The appearance of the prepuce is characteristic. It is split on the inferior aspect and situated dorsolaterally, forming a hood over the glans. The latter is often somewhat plump, flattened in the antero-posterior direction, and furnished with a groove on the under side or, more rarely, with the fossa navicularis ending in a blind pocket on the tip. The frunulum is absent. Proximal to the abnormal opening, the raphe divides into two more or less well-defined branches extending laterally and terminating on the dorsal aspect of the prepuce, at times in one or two rosette-shaped figures, "les yeux dorsaux" (*Ombredanne* (1932)). Between the glans and the opening there is a mucosa-like strip of skin overlying a scar-like band causing a downward curvature of this part of the penis. This curvature is sometimes increased by the tension of a short urethra and overlying skin which also pulls the corpora cavernosa back towards the perineum. The curvature may be complicated by torsion of the body of the penis. In severe cases, the penis is invariably smaller than normal but its smallness is due in part to the curvature as may be shown by successful surgical repair. The scrotum is always cleft when the opening is situated proximal to the peno-scrotal junction, but in mild cases it may be normal or slightly bifid.

In other words, hypospadias is not only a localized urethral defect, but a malformation of the male external genitals, as *Ombredanne* (1932) puts it: "Les formes de l'hypospadias sont les différents degrés de l'aplasie de la face inférieure de la verge".

or immediately proximal to the latter on the distal one fifth of the pendulous part

- (2) *Penile hypospadias* with the opening situated more proximal at any point up to the penoscrotal junction
- (3) *Penoscrotal hypospadias* with the opening in the immediate vicinity of the penoscrotal junction
- (4) *Perineoscrotal hypospadias* with the opening between the two halves of the cleft scrotum or behind it

In classifying a case it is important to consider the situation of the opening in relation to the proximal part of the genitals without trying to straighten the curvature of the penis. If that is attempted the opening is pulled forward the urethra is tightened and this gives a false impression of a milder case. No such regard could be paid in a classification based on case records. In the majority of cases however the classification did not cause major difficulties but it cannot be ruled out that exceptional cases may perhaps have belonged to one of the neighbouring groups.

To designate the morphological transitions between normal genitals and hypospadias the following terms were used

*Low seated opening* The opening is situated on the glans. It may be intranavicular but it is separated from the fossa navicularis by a transverse fold. The prepuce is normal or slightly cleft.



Fig. 1

Juxtaglandular hypospadias bordering on penile hypospadias. Stenosis of opening



Fig 2

Penoscrotal hypospadias



Fig 3

Perineoscrotal hypospadias

**Short urethra** The penis is flexed downwards but the opening is of a normal situation. The prepuce may be slightly cleft.

### Diagnosis

As a rule the characteristic appearance of the malformation makes the diagnosis an easy matter. There have been cases, however, in which patients with hypospadias have spent a short or long period of their lives as girls, because an erroneous sex diagnosis has been made at birth (Neugebauer (1908) Kovacs (1912)) an error which has been made in Denmark too (Sand (1910)).

When hypospadias is associated with undescended testes there is a possibility of erroneous diagnosis. As emphasized by Sand (1940) exploratory laparotomy is required to determine the sex with certainty. This opinion is shared by Hooks (1949). At about the same time he received two patients with hypospadias and bilateral cryptorchidism. Exploratory laparotomy showed the gonads to be ovaries in both cases. This made him assume a more active attitude in examining his patients with hypospadias and in the course of a fairly short time he diagnosed one case of true hermaphroditism (with a left sided ovary and a right sided testis). Another case not yet completely examined was believed to have ovariolestes.

To-day an exploratory intervention involves a very slight risk. It is therefore probably the best thing to ascertain the nature of the gonads

before undertaking plastic repair of the genitals in cases of hypospadias associated with uni- or bilateral cryptorchidism.

Injection of gonadotrophin at the age of puberty may perhaps show the trend of the development (Diaz (1943)) It must be mentioned in passing that injury may lend the genitals the exact appearance of hypospadias

### *Erroneous Diagnoses in the Present Material.*

In Denmark the risk of a wrong diagnosis in hypospadias is probably slight to-day. The midwives are well educated and physicians are very often in attendance. If an error does happen, there are great chances of making it good at the prophylactic infant examinations, medical examinations of children below school age, and the examinations by the school medical officers.

In one case of the present series a wrong sex diagnosis was made in 1928

*Case with wrong sex diagnosis (the proband in Pedigree 77)* At birth the sex was stated to be female. In childhood, however, the parents realized that "something was wrong with the genitals". The patient had no medical examination, was reared as a girl and attended a girls' school. About the age of 14, however, the patient became strangely coarse, and when the sexual desire awakened it was directed towards girls. The patient was very unhappy, believed for a time that he was homosexual, but gradually realized that he must be a man. At a medical examination for another reason, the physician noticed the genital condition and took action. An application for a male



*Fig. 4*

Patient with penoscrotal hypospadias. Probe in the urethra. Penis partly erected. The patient was reared as a girl.

name was filed (through Professor Sand of the University Institute of Forensic Medicine) and granted. The patient was then admitted to hospital for plastic surgery.

Admission examination. The 19-year-old patient is somewhat below medium height, build and hairing masculine.

External genitals (Fig 4). Penis greatly flexed downwards and gives the appearance of being rather small, but the corpora cavernosa are well developed. The penis is situated between the two halves of a slightly cleft scrotum. The prepuce is most developed on the dorsal aspect, absent on the under surface. The glans is cleft on the under side. The orifice is situated between the anterior part of the scrotal halves. No rudimentary vagina. Testes normal on palpation, with epididymides and vasa deferentia, and situated in the scrotum.

Digital examination of the rectum. An organ suggesting the prostate is palpable.

Only one case of pseudovaginal hypospadias occurred in this series. This type differs from the others by the persistent rudimentary vagina. Morphologically it must therefore be considered a special variety which cannot be included in the proband material as a whole. As the patient however, is living as a woman, the case history will be briefly reported.

*Patient with pseudovaginal hypospadias living as a woman.* (The proband in Pedigree 174). The patient (Fig 5) had lived all the time as a woman but at puberty the breasts failed to develop, instead growth of heard set in. The patient denied having any libido, had been engaged (as the female partner) for a time. Recently nodules had developed in both groins.

On admission, at the age of 29, the patient gave a masculine impression. The voice was deep and the breasts undeveloped. Hairing masculine with vigorous growth of beard and hairy chest. Muscles well developed.

External genitals. Phallus 5 cm in length, as thick as the little finger. Two genital folds dilated by nodules, as large as pigeon's eggs, which felt like testes with epididymides. The opening of the urethra was between these folds. Behind the opening, there was a rudimentary vagina, about 2 cm deep ending in a blind pocket.

Digital examination of the rectum revealed a band shaped structure extending from the floor of the rudimentary vagina towards the abdomen.

Exploratory laparotomy showed a pelvis of masculine appearance, with deep rectovesical pouch, but no signs of a uterus or its appendages. The gonads were seen on both sides. They were somewhat atrophic testes, which otherwise looked normal, with epididymides and vasa deferentia. Biopsies were obtained from both sides, and histological examination showed testicular tissue with atrophy, fibrosis, and an increased number of Leydig's cells. The patient was made acquainted with the condition. A change of name was proposed and the patient agreed, but after having been referred to Professor Sand, "she" changed her mind and went on living her life as a woman. When seen later, the patient stated that the growth of beard bothered her most.

The patient has a sister who was hospitalized and showed the same condition. In this case however the testes had not descended.

In addition there is a case of real diagnostic error, a case of true hermaphroditism diagnosed as hypospadias.

*True hermaphroditism diagnosed as hypospadias* (the proband of Pedigree 175) Hospitalized for the first time at the age of six showing downward curvature of the penis with a dorsal prepuce. The glans was cleft on the under side and from this side a band shaped structure extended to the urethral opening which was situated on the anterior aspect of the partly cleft scrotum. The right testis was in the scrotum whereas the left one was in the superficial inguinal ring. The downward flexion of the penis was corrected. At the age of 13 the patient had left sided orchidomobilization and herniotomy. The testis was found to be inverted outside the superficial inguinal ring. There was a congenital hydrocele the abdominal part of which contained omentum. Following isolation of the spermatic cord up to the deep inguinal ring the testis could be mobilized almost down into the scrotum.

On several subsequent occasions the patient had plastic operations to re-construct the urethra.

At the age of 15 the patient returned because of increasing swelling of the left half of the scrotum. Puncture yielded a hemorrhagic fluid. A tumor was



Fig 5

Patient with pseudo vaginal hypospadias living as a woman



Fig 6

A case of true hermaphroditism. Testis on the right ovary on the left. Tunnel shaped urethral opening on the anterior aspect of the scrotum.

palpable in the scrotum. The patient was admitted and had exploratory laparotomy which showed the "tumour" to be a uterus. In addition, a Fallopian tube and a normal ovary with follicular cysts. The bleeding was presumably been an ovulation bleeding. The right gonad was now exposed and proved to be a normal testis with epididymis and vas deferens. Biopsy specimens of the gonads on both sides showed ovarian tissue on the left and testicular tissue with spermiogenesis on the right.

A few weeks later the uterus, tube and ovary were removed.

Examination of the operative specimen revealed a small cavity in the uterus with endometrium in the early proliferative phase, a normal tube and a normal ovary.

This case raises the question whether the proband material may be considered uniform despite the even transition as regards the appearance of the external genitalia. In several cases the hypospadias may have been combined with undescended testes and the true nature of the gonads is not known.

### *Writer's Morphological Studies*

#### *Incidence of Retained Testes in Hypospadias*

The incidence of undescended testes in the various degrees of hypospadias has not been numerically elucidated. An analysis of this nature is of particular interest to the present study since bilateral cryptorchidism is tantamount to sterility (Torben Svendsen Hansen (1945)). An increased incidence of cryptorchidism in hypospadias would therefore contribute to reducing the fertility and consequently influence the transmission of morbid genes, if any.

Moreover it would be interesting to ascertain whether an increased incidence of this phenomenon is peculiar to the severe forms of the condition, as this might justify a sharper division of severe from mild cases.

This analysis was based on the case records for patients with hypospadias admitted to the University Hospital, Copenhagen, Surgical Departments C and D, the Copenhagen City Hospital, Surgical Departments I and V, the Bispebjerg Hospital, Surgical Departments A and D and the Surgical Departments of the Aarhus University Clinic and the Aarhus County Hospital. The material includes also cases of hypospadias occurring among the probands' relatives. The patients used later as probands were seen personally, whereas in the remaining half, mainly mild cases, — the data are based exclusively on case records.

The material is set out in Table I which shows that in a certain number of cases the records do not state whether the testes had descended



to the scrotum. As these cases are counted as normal, the calculated incidence of cryptorchidism represents minimum values. The material is classified not only according to the degree of hypospadias, but also according to age at the time of examination, since undescended testes often descend spontaneously during boyhood.

The results may be compared with other Danish studies of cryptorchidism at various ages. Perusing the record cards of the School Medical Officers, *Engberg*, in 1918 found 1535 cases among 34,000 boys aged 6-7 years, i.e. an incidence of 4.51 % in this age group. In *Engberg's* opinion, however, the incidence is somewhat lower; he believes that some of the cases have been pseudocryptorchidism. A follow-up exami-

Table 1.

Incidence of cryptorchidism in hypospadias. The material is classified according to the degree of hypospadias and the patient's age.

Degree of hypospadias	Testes in scrotum	Lacking data	Undescended testes				Total cases	Expected number with undescended testes
			right	left	both	total		
<i>Juxtaglandular</i>								
0-9 yrs	75	24	2	6	3	11	110	4.95
10-17 yrs	37	4	—	—	—	—	21	0.32
18 and over	31	9	—	—	—	—	40	0.20
Total	123	37	2	6	3	11	171	5.47
<i>Penile</i>								
0-9 yrs	11	1	1	1	2	4	16	0.72
10-17 yrs	4	—	—	—	1	1	5	0.08
18 and over	6	—	—	—	—	—	6	0.03
Total	21	1	1	1	3	5	27	0.83
<i>Penoscrotal</i>								
0-9 yrs	12	1	1	4	7	12	25	1.13
10-17 yrs	4	—	1	—	3	4	8	0.12
18 and over	15	2	—	—	1	1	18	0.09
Total	31	3	2	4	11	17	51	1.34
<i>Perineoscrotal</i>								
0-9 yrs	8	—	—	3	2	5	13	0.59
10-17 yrs	3	—	—	2	1	3	6	0.09
18 and over	2	—	2	—	2	4	6	0.03
Total	13	—	2	5	5	12	25	0.71
<i>Total cases</i>								
0-9 yrs	106	26	4	14	14	32	164	7.38
10-17 yrs	28	4	1	2	5	8	40	0.60
18 and over	54	11	2	—	3	5	70	0.35
Total	188	41	7	16	22	45	274	8.33

nation of a large number of these boys after they had passed their 10th year revealed spontaneous descent in two thirds. Perusal of the medical conscription protocols (cryptorchidism is a ground for rejection) *Fagberg* (1948) and *Torben Svend Hansen* (1945) found 527 cases among 108,113 men ranging in age from III to 30—that is an incidence of 4.86 per thousand. From a report on the work of the Baby and Child Health Stations (*Gortz* (1951)) an estimate may be formed of the incidence of cryptorchidism in the youngest age groups. In 1948 a total of 10,402 children were examined at the Child Health Stations; of them 108 showed cryptorchidism which is an incidence of 2.08 % provided that half the children are boys. At the Baby Health Stations where babies under one year of age are examined the corresponding incidence was only 1.12 %. These values must be regarded with some reserve if only for the reason that the mothers can have the prophylactic examinations carried out also by their own physicians if they want them done at all. This material is therefore selected and the criteria of selection are unknown.

On the basis of the studies mentioned the following normal values will be used in the present paper:

0—9 years 4.5 % with undescended testes  
 10—17            1.5 %  
 18 years and over 0.5 % with

From these normal values which must be considered rather high the expected number of cases of hypospadias with undescended testes was calculated for the individual groups. The results are given in the first column of Table 1.

Table 2  
 Increasing incidence of undescended testes with increasing severity of hypospadias

	$\chi^2$	1 in $10^6$	$p_1$ in $10^6$ $p_2$ in $10^6$
Juxtuglandular hypospadias	2.0	6.43	14.51 2.71
Penile hypospadias	6.0	18.52	47.34 5.43
Perineoscrotal hypospadias	16.7	33.33	54.27 17.39
Perineoscrotal hypospadias	16.9	48.00	74.24 22.82
Total cases	5.4	16.42	24.40 10.58

Table 2 shows how many times the actual findings exceed the expected values  $\left(\frac{x}{n}\right)$  in the different varieties of hypospadias. In addition the incidence  $P\left(\frac{x}{n}\right)$  and its upper and lower confidence limit  $P_u$  and  $P_m$  were calculated according to the formula

$$\frac{1}{n+1} \left( x + 4.75 \pm 3 \sqrt{\frac{x(n-x)}{n} + 2.25} \right) \quad \text{Kemp (1942) } 1 < p < 3$$

The incidences found do not apply to all series of hypospadias as the patients' age influences the incidence of cryptorchidism. In the groups penile perineoscrotal and penoscrotal hypospadias however the values show that the incidence of retained testes is increased in hypospadias the lower confidence limit being higher than the 4.5 % in the youngest age groups of the normal series.

In juxtapositional hypospadias the lower confidence limit is lower than 4.5 %. The actual number with undescended testes was therefore compared with the expected number by means of the  $\chi^2$  test. The result is  $0.01 < p < 0.02$  ( $f = 1$ ,  $\chi^2 = 5.76$ ). The difference is not significant but extremely probable particularly when considering that the normal values are rather high.

In 48.9 % the cryptorchidism was bilateral. In a series of 256 cases *Bjerre* (1935) found 36.7 % bilateral. In series of this small size the difference is not real. As *Bjerre* found only 16.3 % bilateral among 900 cases from the literature the incidence of bilateral cases in hypospadias may still be increased.

It will be seen that an increased incidence of cryptorchidism is characteristic of all degrees of hypospadias increasing with increasing severity of the hypospadias. This quantitative difference does not afford any justification for a morphological division of the mild and severe varieties.

The increased incidence of cryptorchidism and the possible relative increase in bilateral cryptorchidism entails a reduced fertility in hypospadias particularly in the most severe degrees.

## Chapter 2

### INCIDENCE

#### *Previous Investigations*

Hypospadias is a fairly common defect. Various authors have analysed the incidence but the results have varied owing to inadequate selection and a too small size of the materials in several instances.

The highest incidence has been reported by *McGrea* (1940). Among 150 men he found hypospadias or a low seated urethral opening in 4 %. The material is too small and nothing is stated as to how it has been collected.

*Howry* (1919) found 2 % among 10 000 soldiers suited only for limited military service. It cannot be ruled out that hypospadias may have been the cause why a soldier has been declared unfit for full military service. This material is therefore possibly selected. For the same reason the analyses of the incidence among patients with urinary tract diseases are of little value. In series of this category *Barragan* (1911) has found 26 cases among 14 000 and *Burchhardt* (according to *Schneider* (1928)) 22 among 1849.

The best materials are *Rennes* (1831) 3000 recruits among whom 10 cases of hypospadias occurred and *Campbell's* (1947) post mortem series of 12 280 children with an incidence of hypospadias of one in 1100 boys.

*Hofmoller's* finding (cited by *Langstein* (1910)) of only 13 cases in 104 446 children (the largest series reported hitherto) must be due to insufficiently thorough examination.

*Neugebauer's* (1908) incidence of one in 1000 is presumably merely an estimate and it is not clear how *von Schurer* has arrived at his rate of one in 60 births.

The incidence of hypospadias in Denmark has not been analysed from a report on the work of the *Prophylactic Child and Baby Health*

Stations (Gartz (1951)) it is apparent that during the first year of their existence — 1948 — 17 cases of hypospadias were found among 8242 babies under one year of age (Baby Health Stations) and 7 among 10,402 children aged 1—7 (Child Health Stations). Since, however, the prophylactic child examinations may be carried out by the child's own physician and are moreover voluntary, unknown factors may have caused a selection of the material. Nevertheless, a certain estimate may be formed of the incidence, which is rather more than 4 per thousand among the younger age group and less than 2 per thousand in the older group. This presupposes that half the children examined are boys. This difference in the incidence may be due to the small numbers involved, but it may also be due to incongruence between the two series.

### • *Writer's Investigations*

#### *Determination of the Incidence among Newborn Babies*

To this end, the writer chose the case records from Lying-In Department B, Rigshospitalet, Copenhagen from the year it was opened in 1910 up to and including 1915. In this department the newborn babies are examined for congenital defects at birth, on the rounds on the following day, and immediately before discharge. This series was, therefore, thoroughly examined. Nevertheless, all the mild cases had not been entered on the diagnostic card index, and therefore every record had to be perused.

A total of 60,680 records were perused. Among them there were 27,613 boys alive on discharge, 90 had hypospadias. The cases are described only in brief outline. Often the case records give merely the diagnosis. It cannot be ruled out that one case has been a low-setted orifice and another one a short urethra.

Including the last two cases, the incidence among the living discharged boys aged about 10 days (when mother and child are usually discharged) is one in 307 or 3.26 per thousand.

$$\left. \begin{array}{l} p_s \text{ per thousand} \\ p_m \text{ per thousand} \end{array} \right\} = \begin{array}{l} 4.46 \\ 2.38 \end{array}$$

(calculated according to the formula (Kemp (1942) p. 53)

$$\left. \begin{array}{l} p_s \\ p_m \end{array} \right\} = \frac{1}{n+9} \left( z + 4.5 \pm 3 \sqrt{\frac{z(n-z)}{n} + 2.25} \right)$$

### *General Validity of the Incidence Found*

Most of these children were born of young, unmarried women who have a preference for admission to this department. The material is, therefore, selected. If Büchtz (1950) theory, viz that babies with hypospadias are more often born of young than of older women, holds good, the incidence found in the present material must be higher than among all newborn boys. As shown later, the author is not in a position to confirm Büchtz's theory, and no regard was paid to this selection of the series.

There does not seem to be any reason to presume that patients with hypospadias are subject to a particularly high mortality. *A priori*, however, it cannot be ruled out that an increased mortality may be caused, in part by the lesion itself and in part by a possible inferior general condition of the malformed babies. If so, the incidence must decrease with advancing age, and that found in the present material becomes too high.

Since the unmarried mothers are registered only by number (the names being entered in secret protocols) it was impossible to trace these 90 children in order to ascertain their viability. Their birth weight did not differ significantly from that in normal series (*vide infra*). In this respect, therefore, children with hypospadias do not show an inferior general condition. To procure a material with which to compare the incidence of hypospadias among the newborn, all boys aged 7-14 in the municipal schools of Esbjerg on the west coast of Denmark were examined with a special view to hypospadias. The defect was found in 13 out of about 2050 boys (Jacobsen (1949)). The material is not particularly large, but it accords well with that from the Lying-in Department, the incidence is 4.47 per thousand,  $p_1$  calculated per thousand being 0.87 and  $p_{95}$  1.95.

Hypospadias may pave the way for urinary tract infection, as the stenosis of the urethral opening, present particularly in mild cases, may give rise to dilatation of the urinary tract. Campbell (1943) examined 152 children under 14 years of age with stenosis of the urethral opening. Of them 98 % were congenital and some of these patients had hypospadias. Urinary tract infection was present in 25 %. Fruhmann & Sternberg (1930) have reported a case of hypospadias with stricture of the urethral orifice. The patient succumbed to an ascending urinary tract infection.

Several patients of the present series had stricture and urinary tract infection. Only one patient succumbed to a urinary tract lesion.

*Juxtaglandular hypospadias with stricture of the urethral orifice and fatal kidney disease* (the proband of Pedigree 118). The patient was admitted at

the age of 33. For the past 2 or 3 years he had been complaining of fatigue, headache and swelling of the legs. About one year before admission nephritis was diagnosed and treated with dietary measures. The patient was admitted because of fatigue which except for brief periods had incapacitated him for the past year.

On admission the patient looked quite well. He had mild hypospadias with a small opening. The urinary stream was thin. Clinical examination revealed no other abnormalities. No oedemas. Temperature 37.5° C. B.P. 170/125. Urine contained albumin. Specific gravity about 1.010 increasing in the concentration test to 1.015 and decreasing on water tolerance test to 1.007.

With some difficulty catheterization was performed with catheter No. 8. It yielded a slightly bloody urine. On microscopical examination the cell findings corresponded to the haemorrhage. No bacteria and no growth upon culture.

Owing to the greatly impaired renal function bilateral decapsulation of the kidneys was performed a fortnight after admission (in March 1924). The kidneys were hard, shrunk and granulated on the surface and there were fibrous adhesions to the capsule.

Postoperative pyrexia and pulmonary symptoms. The patient succumbed three days after the operation.

*Necropsy:* Chronic nephritis, sequelae of nephrotic syndrome, bronchopneumonia, oedema of the lungs and pleurae, chronic fibrinous pleurisy, cystitis, hypospadias. Dilatation of the renal pelvis or ureters was not observed.

In this case the diagnosis was presumably glomerulonephritis. The patient had not at any time exhibited signs of urinary tract infection. He had no bacteriuria or dilatation of the urinary tract. Therefore hypospadias associated with a slight stenosis of the urethral orifice can hardly have been responsible for the fatal issue.

It is worth considering also whether an increased mortality may be caused by malignant degeneration in the retained testes which are unduly common in hypospadias (cf Chapter 1). Carroll (1949) has severely criticized the statistical investigations which have shown a relatively common malignant degeneration in retained testes. He has moreover studied the problem by sending questionnaires to a large number of urologists. He concludes that it has not been sufficiently proved that malignant tumours are particularly common in retained testes, that malignant tumours of the testes are rare, that they are extremely rare in cryptorchidism. Accordingly there does not seem to be any reason to presume that this may lead to an increased mortality among patients with hypospadias. Seminoma occurred in only one case of the present series.

*Perineoscrotal hypospadias with unilateral cryptorchidism.* Abdominal seminoma of unknown origin. (The proband of Pedigree 141). A 24 year old man was admitted with the diagnoses perineal hypospadias, inversion of the right testis, right sided inguinal hernia.

The penis was rather small and downward flexed with dorsolateral foreskin which was cleft on the under surface. The urethral orifice was situated between the two halves of the cleft scrotum. The left testis was normal on palpation and situated in the scrotum whereas the right one was impalpable.

The penis was straightened and orchidomobilization was performed on the right. The right testis was small atrophic and inverted at the superficial inguinal ring.

When 5 months later the patient was readmitted for plastic reconstruction of the urethra, the right testis was at the superficial inguinal ring slipping in and out. Moreover there was oedema of the right leg. The patient complained of a feeling of tension in the abdomen. No abnormality was detected by palpation or digital examination of the rectum. Two months later a swelling was found in the lower abdomen. Median inferior laparotomy revealed a large tumour which surrounded the iliac vessels on the right. The tumour which moreover had invaded the caecum and the lower portion of the ileum was inoperable. Histological examination of a biopsy specimen showed seminoma. The tumour yielded to X radiation a total of 2800 r.

At follow up three years after the operation there were no signs of recurrence. The patient complained of attacks of subacute intestinal obstruction and the circumference of the right lower limb had increased by 5 cm.

The point of origin of this tumour is unknown. No tumour was at any time palpable in the normal left or in the atrophic right testis.

Accordingly this material affords no evidence that an inferior genital condition, urinary tract infection or malignant testicular growths should give rise to essentially increased mortality among patients with hypospadias. The incidence found among the newborn — 3.26 per thousand — will therefore be used to represent the incidence among the entire male population.

### *Incidence of the Various Degrees*

#### *Previous Investigations*

The mild degrees are by far most common. All *Rennes* (1831) cases were mild and so were most of *Mowry's* (1919). According to *Higgins* (1947) 70—75 % are of the glandular variety. These values are presumably derived from a hospital series and record well with *Barragan's* (1911) and *Burchardt's* (cited by *Schneider* (1929)) findings of the glandular variety in 14 out of 26 and in 13 out of 22 patients respectively.

#### *Writer's Investigations*

Table 1 (p. 20) gives the incidence of the various degrees in a series consisting predominantly of hospital cases. About 62 % were jugular glandular. Perineoscrotal hypospadias made up only about 9 %. This



does not however represent the incidence among the general population since it must be presumed that only the severe cases are hospitalized

In the series from I ying in Department B it is not possible to classify the hypospadias in all cases. The case records which state only the diagnosis often add an adjective such as mild slight some or marked. All the cases classified as penoscrotal or perineal however are thoroughly described.

Since a follow up examination was out of the question the author tried to identify the cases with the patients from the surgical series by their — and in some cases the mother's — date and place of birth. Two instances described as slight hypospadias and three as mild could be classified among the juxtaglandular cases. One case called hypospadias was identified as a case of penile hypospadias. None of the non classified cases could be identified as one of the two severe groups.

*Table 3*

Classification of 90 cases of hypospadias among newborn boys

Short urethra	1
Low seated orifice	1
Juxtaglandular hypospadias	29
Mild hypospadias	8
Slight hypospadias	23
Some hypospadias	3
Hypospadias	8
Penile hypospadias	2
Marked hypospadias	4
Penoscrotal hypospadias	5
Perineoscrotal hypospadias	6

The exact incidence of the different degrees cannot be decided on the basis of the diagnoses listed in Table 3. At an estimate the juxtaglandular cases made up about three quarters, the penile ones about one eighth and the penoscrotal and perineoscrotal together about one eighth.

## Chapter 3

### FERTILITY

#### *Previous Investigations*

No report seems to have been published of the fertility in hypospadias. There is reason to presume, however, that in the severe degrees it is reduced. However, deformities severe enough to give occasion to a wrong diagnosis need not be tantamount to absolute sterility. *Neugebauer's* collected work from 1908 reports the case of a hypospadiarian living as a woman who impregnated her fellow servant who gave birth to a boy with hypospadias.

In many authors' opinion (*Mayo* (1901) *Mowry* (1919) *Ombredanne* (1932) *Marx* (1938)) the fertility is reduced even in the glandular variety. *Mayo* (1901) goes as far as stating that the majority of the patients are impotent. In *Ombredanne's* (1932) opinion the fertility is reduced because the sperm is not slung towards the os externum uteri but instead deposited in the posterior fornix. No doubt these theoretical considerations have led to an incorrect result. At least part of the present series with glandular hypospadias published in 1948 (*Rahbek Sørensen*) did not show reduced fertility.

In the most severe cases the fertility is influenced by several factors. Complicating bilateral retention of the testes will prevent reproduction. Downward flexion of the penis makes coitus difficult. If the urethral opening is at the scrotum it may be impossible to deposit the sperm in the vagina. The two last mentioned difficulties may be improved by surgery. This is no doubt what made the two German workers *Marx* (1938) and *von Schurer* (1939) propose that reconstruction of the urethra be performed only if the patient submits to sterilization so as to prevent the transmission of the morbid gene.

### *Writer's Investigations*

Owing to the marked morphological differences between mild and severe cases between treated and untreated a numerical evaluation of the fertility in a given series is less interesting than an evaluation of the fertility in the various degrees and of the significance of treatment.

The writer therefore investigated whether hypospadias marry as often as others. Moreover the fertility of the married patients will be evaluated while due regard is paid to the extent of the defect and the result of treatment if any.

### *Frequency of Marriage Among Hypospadias*

The series includes 77 patients — probands and their relatives — aged 20 or over. These cases are classified in Table 4 according to civil status, age and degree of deformity. This table also gives the expected number of married and single persons in the various groups of severity and age groups. The expected values were calculated on the basis of the number of single men and the total number of men in the Danish population at the 1940 census (*Statistique du Danemark 1945*).

Despite the small figures involved the table shows a striking conformity between the actual and expected number of married and single patients in each of the four groups of hypospadias. There are 30 single patients as against the expected 30.34.

In other words hypospadias marry just as often as other men and the degree of the malformation does not appear to influence the frequency of marriage.

### *Sexual Function*

The married patients were questioned as to whether coitus caused difficulties and whether it could be accomplished to the satisfaction of both partners.

Three patients had complaints in this respect.

(1) The proband of Pedigree 129. A man aged 34 who married before his penoscrotal hypospadias had been treated. Since sexual intercourse was carried out with difficulty and little satisfaction to either partner the patient was admitted for surgery after two years of married life. A successful surgical correction and reconstruction of the urethra was performed. At follow up about two years later the patient reported that now coitus could be performed without difficulty and to the satisfaction of both partners.

(2) The proband of Pedigree 143. A 39 year old man with perineoscrotal hypospadias. Surgical correction had been tried in several hospitals. At



follow up the penis was somewhat small and flexed downward by a scar like band. The urethral opening was at the penoscrotal junction. The patient complained of difficulty in performing the sexual act.

(3) The proband of Pedigree 162. A 35 year old man with previously treated penoscrotal hypospadias. At follow up the penis was rather small and with marked downward flexion due to scar like bands. The newly formed urethra opened at the corona. A fistula at the penoscrotal junction. The patient complained of difficulty in performing the sexual act due to the flexion. His wife hardly ever obtained orgasm in the patient's opinion because of the small size of the penis.

In all three instances the difficulty in performing the sexual act was due to a rather marked flexion of the penis. Many of the remaining patients had had surgical correction of severe flexion before marrying but even so several had slight to moderate flexion of the glans or the penis (cf. Tables 5—8). According to the patients' statements such flexion has not caused any discomfort. Perhaps these statements should be accepted with some reserve especially as regards the wife's satisfaction. It seems however that the matrimonial relations and sexual intercourse of hypospadias do not differ essentially from normal once severe flexion has been corrected. The fertility then depends only on the more or less adequate deposition of the sperm and on the quality of the latter.

### *Fertility and Morphology*

In an endeavour to evaluate the fertility of each degree separately each group was tabulated separately. The tables (5—8) give each patient's age, morphological features, number of children and abortions and by comparison the number of children begotten by his normal married brothers.

### *Juxtaglandular hypospadias*

The cases are presented in Table 5 which comprises 24 patients. All but three had children. Two of the last mentioned patients' wives however had had miscarriages, one of them twice because of intoxication of pregnancy. This couple did not want another pregnancy. One married man, aged 50, was childless against his will.

The number of children ranged from 1 to 8, averaging 2.28. In comparison 23 normal brothers had an average of 1.70 children each.

No difference in fertility could be demonstrated between the treated and untreated cases.

### Penile Hypospadias

Table II presents 6 patients all of whom had children ranging in number from 1 to 3 and averaging 1.67. Nine normal brothers had on the average 1.56 children each. In this group no difference was found in the fertility of treated and untreated cases (or cases in which the treatment had been unsuccessful).

### Penoscrotal Hypospadias

Of the 12 patients listed in Table 7 four had children. Moreover the wife of a 24 year old patient had had two miscarriages. The wives of seven patients had never been pregnant. In one of these cases the sterility was due to bilateral retention of the testes.

The four fertile patients had 4, 4, 2 and 1 children respectively. The average number of children per patient was 0.9. Five normal brothers had an average of 1.8 children. All the patients had been treated. Among the fertile ones the reconstruction of the urethra had been a failure in two (with 4 and 2 children) and partially successful in two (with 4 and 1 children).

### Perineoscrotal Hypospadias

This group comprises only five patients who are listed in Table 8. None of the patients had children. In three of these cases the sterility is explained by bilateral cryptorchidism. In addition one patient with left sided cryptorchidism had been hospitalized at an adult age because of right sided epididymitis. In the remaining case the testes were normal but the urethral opening was situated between the two halves of a cleft scrotum.

In juxtaglandular hypospadias the fertility appears to be normal and in the penile variety it is not definitely reduced. In these two varieties treatment does not appear to influence the fertility.

In penoscrotal cases the fertility must be presumed to be reduced in untreated cases or in those in which treatment has failed although the possibility of procreation is present. This series does not permit conclusions regarding the influence of successful treatment on the fertility as it dates several years back and therefore includes few successful corrections.

Table 5.  
*Juxtaglandular hypospadias*  
Fertility and morphological features

P. degree No Status in family	Age	Treated	Flexion	Site of urethral opening	Fistula	Site of testis	Number of children	Number of in- carnages	Number of brothers without hypos- padias	Number of brothers children	Number of children per brother
2 Father	33	no	Slight of glans	Corona	None	Scrotum	3	3	2	1	0.5
6 Paternal grandfather	80	no	None	Corona	None	Scrotum	7	0			
8 Paternal uncle	55	no	Slight of glans	Corona	None	Scrotum	4	0	4	12	2.0
9 Proband	71	no		Corona	None	Scrotum	8	0	2	1	0.5
23 Proband	22	yes	Slight of glans	Glans	None	Scrotum	0	1	0		
50 Proband	23	no	Slight of glans	Corona	None	Scrotum	1	0	0		
51 Proband	44	yes	Slight of glans	Glans	None	Scrotum	0	0	0		
12 Maternal grandfather	52	no	None	Corona	None	Scrotum	2	0	2	0	0.0
12 Maternal grandfather's brother	52	no	None	Corona	None	Scrotum	1	0	2	0	0.0

[illegible]



*Table 6.*  
*Penile hypospadias*  
Fertility and morphological features

Pedigree No Status in family	Age	Treated	Flexion	Site of urethral opening	Pistula	Site of testes	Number of children	Number of mis- carriages	Number of brothers without hypos- padias	Number of brothers children	Number of children per brother
6 Paternal uncle	48	no	Slight of penis	Distal part of body	None	Scrotum	1	0	4	6	15
57 Proband	29	yes	Slight of penis	Glans	None	Scrotum	2	0	1	2	20
66 Proband	36	no	Slight of distal part of body	Distal part of body	None	Scrotum	1	0	3	3	17
123 Proband	34	yes	Slight of glans	On glans	None	Scrotum	2	0	1	1	10
127 Proband	36	yes	Slight of glans	Distal part of body	None	Scrotum	1	0	0		
150 Proband	38	yes		Not followed up			3	0			

**Table 7**  
**Penoscrotal hypospadias**  
**Fertility and morphological features**

Pedigree No. Status in family	Age	Treated	Erection	Site of urethral opening	Location	Site of testes	Number of children	Number of mis- carriages	Number of brothers without hypos- padias	Number of brothers et al.	Number of children per brother
60 proband	47	yes	Moderate of penis	Penoscrotal junction	None	Scrotum	4	0	2	8	40
73 proband	28	yes	Moderate of penis	Corona	Pinhead at radix	Scrotum	1	0	0		
72 proband	20	yes	None	Glans	1 small at radix	Scrotum	0	0	0		
■ proband	43	yes	Moderate of penis	Penoscrotal junction	1 small in pend part	Operated bilateral cryptorch	0	0	1	0	0
80 proband	30	yes	Slight of penis	Glans	Vestige of urethra at glans	Scrotum	4	1	1	1	1
93 proband	24	yes	Slight of penis	Middle of pend part	Small near the tip	Scrotum	0	2	0		
128 proband	30	yes	Slight of penis	Radix	None	Scrotum	2	1			
129 proband	34	yes	None	Corona	None	Scrotum	0	0	0	0	0
132 proband	40	yes	Slight of penis	Glans	One at radix	Scrotum	0	0	1	0	0
133 proband	27	yes	None	Near radix	2 on middle of pend part	Scrotum	0	0	0		
162 proband	70	yes	Marked of penis	Corona	None	Scrotum	0	0			
164 proband	39	yes	Slight of penis	Radix	One at radix	Scrotum	0	0			

Table 8

*Pertneoscrotal hypospadias*

## Fertility and morphological features

Patient No. Status in Family	Age	Treated	Flaccid	Size of urethral opening	Location	Size of testes	Number of children	Number of mals carriage	Number of brothers without hypospadias	Number of brothers with hypospadias	Number of children per brother
138 proband	24	yes	Slight of penis	Glands	Very small in perineum	Bilateral cryptorch	0	0	0	0	
139 proband	28	no	Marked of penis	In a cleft scrotum	None	Bilateral cryptorch	0	0	0	0	
142 proband	31			Not followed up							
143 proband	32	yes	Marked of penis	In a cleft scrotum	None	Bilateral cryptorch	0	0	0	0	
172 proband	37			Not followed up		Scrotum	0	0	1	1	10
						Left sided cryptorch sequence of right sided epididymitis	0	0	0	0	

In perineoscrotal hypospadias the fertility is greatly reduced if only because of the high incidence of bilateral cryptorchidism. It is difficult to say whether surgical treatment might render some of the patients fertile.

From the point of view of genetics this means that the incidence of severe cases among the probands' fathers is lower than might be expected according to the mode of inheritance.

## Chapter 4.

### PREVIOUS STUDIES ON THE HEREDITY OF HYPOSPADIAS

The heredity of hypospadias has never been elucidated by a proband study. According to case reports, however, it is considered to be transmitted by irregular dominance (*Kemp* (1940), *Weitz* (1940), *Gates* (1946))

*Kemp*, in 1940, collected all familial cases published up to 1909, mainly on the basis of *Bullock's* (1909) and *Neugebauer's* collected works. This revealed that hypospadias had been reported

11 times in 2 brothers,  
7 times in 3 brothers,  
twice in 4 brothers,  
once in 5 brothers,  
9 times in father and son,  
3 times in father, son, and grandson,  
twice in 5 generations, and  
once in 6 generations

Since that time no large families have been reported, but some surgeons (*Ombredanne* (1932), *Loughran* (1948), *Schaefer & Erbes* (1950)) have seen several familial cases.

Reports of two or three cases in the same family are of little interest considering the common incidence of the defect. Large and thoroughly examined families, on the other hand, may give a hint as to the inheritance. The largest family was reported by *Lingard* (1884). He found hypospadias through 6 generations in direct lineage. In this family there was a striking number of cases, even when considering the dominant character of the defect. It is not apparent, however, how many of the patients *Lingard* had seen personally.

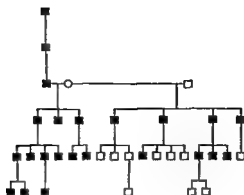


Fig 7

*Lingard's family with hypospadias through 6 generations*

In *Iesser's* family (1889) the inheritance appears to have been by irregular dominance. Only two of the 11 members afflicted had been seen personally. The data regarding the remaining 9 and the 4 persons who were presumed to be affected were given by the mother of the two subjects examined. Although *Iesser* states that this woman was trustworthy, I do not attach much importance to this family, knowing from experience that information about hypospadias in relatives supplied by members of the families is extremely unreliable.

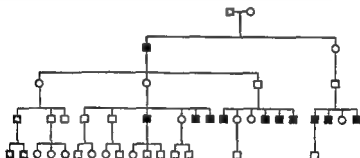


Fig 8

*Iesser's family with irregular dominance*

Also in *Strong's* family (1906) (cited by *Bullock* (1909) with hypospadias in 5 generations the affected members had not been examined personally. The data were supplied by a patient with juxtapapillary hypospadias. Therefore this family also is of little interest.

In several instances, concordant hypospadias has been observed in monozygotic twins (*Lehmann* (1936), *Steiner* (1936), *von Verschuër* (1940), *Rhodes* (1943)). Moreover, *Camerer* (1938) has reported a case of discordance in monozygotic twins.

*Lamy* (1952) has collected a twin material of three pairs of concordant and three of discordant monozygotic as well as of four pairs of discordant dizygotic twins. These twins were part of a twin material exceeding 900 pairs collected from schools and hospitals in Paris.

The studies mentioned above have not definitely established the hereditary nature of hypospadias. Since discordance has been found in monozygotic twins, exogenous factors must play a certain aetiological rôle. Exogenous factors may be imagined to act upon both twin foetuses at the same time and thus make for concordance which in that case is independent of mono- or dizygosity. *Lamy's* twin material indicates the aetiological rôle of heredity, as concordance was encountered in monozygotic, but not in dizygotic twins. The numbers involved are, however, too small to make the difference statistically significant.

## *Chapter 5*

### MODE OF COLLECTING AND EXAMINING THE PRESENT SERIES

In order to elucidate the heredity of hypospadias the writer collected a proband and a twin material. The incidence found in these series was then compared with that found among the newborn and schoolboys (cf Chapter 2)

#### *Selection of Probands*

As probands the writer selected patients admitted to Surgical Departments C and D of the University Hospital, Copenhagen during the period 1915 to 1945, including a few out-patients. This material was supplemented with cases of penile, penoscrotal, and perineoscrotal hypospadias admitted to Surgical Departments A and D of the Bispebjerg Hospital, Copenhagen, Surgical Departments I and V of the Copenhagen City Hospital, and the surgical departments of the Aarhus County Hospital and the Aarhus University Clinic.

This proband material does not represent a cross section of the population, not merely because in the last six departments the mild cases were excluded, but also because a hospital material is bound to include more severe cases than mild. The material was selected in this way, because the most severe cases are of most eugenic interest.

#### *Examination of the Proband Material*

By personal application to each proband or his parents, if he was a child, the writer obtained the family history, examined the proband and asked for permission to apply personally to all male relatives. All the male relatives were then visited and, if they did not refuse, submitted to an examination usually restricted to the external genitals.



Relatives in military service were examined by the medical officers concerned and hospital patients by the hospital doctors. A few relatives wished to be examined by their own physicians and a few living in distant parts of Denmark were also examined by their own physicians.

True the examination of all male relatives was cumbersome and time consuming but it proved necessary as the probands or his parents data very often did not conform to the result of the examination. On the one hand there would be cases in the family about which they had no idea and on the other hand relatives believed to be afflicted proved to have normal genitalia.

### *Effectiveness of the Examination*

The majority of the patients (and parents) were willing to co-operate but a few refused to give me permission to apply to the relatives. In most of these instances the defect had been concealed from the greater part of the family. I did not try to persuade these probands as it is difficult to realize the psychic suffering which might thereby have been inflicted on the often rather sensitive patients. Instead I asked permission to examine the closest relatives who knew about the defect. In this way it proved possible to examine several relatives usually fathers and brothers. Moreover this yielded further data about congenuity. A few exceptional patients or parents however refused to have anything to do with this study. Another few had to be excluded because they could not be traced were adopted or foster children or lived abroad.

Accordingly the material is divisible into three groups

- I 103 families examined
- II 43 families partially examined
- III 27 families excluded

To these 173 families may be added two which in fact do not belong to this material

- IV A family with pseudovaginal hypospadias
- A family with true hermaphroditism

Only 61 % of the families were examined as thoroughly as might be desired but there is no reason to believe that any selection of families with familial or with non familial occurrence of the defect has taken place. Naturally enough a relatively large number of the patients with severe deformity did not want to have their relatives examined.

Some of the relatives refused to be examined and were therefore ruled out. From Table 9 it will be seen how many relatives refused to

have the examination and how large a percentage they made up of those who might have been examined. This table furthermore contains a group called Others not examined comprising relatives living abroad sailors etc and a group of deceased relatives. There is no reason to believe that this has made for a selection of malformed or non malformed relatives.

It is evident from the table that the percentage of refusal was higher among distant than among close relatives. This accords with the experience that the more distant relatives are less interested in the study. There is no reason to believe that the very persons who refused to be examined should be hypopadians.

Table 9

Number examined and not examined in the various categories of relatives

	Examined	Refused to examine	Others not examined	Deceased
Fathers	96	1 (1.03 %)		0
Brothers	11	1 (1.19 %)	1	12
Grandfathers	81	3 (3.57 %)	10	112
Paternal or maternal uncles	277	15 (5.14 %)	25	78
Cousins	563	34 (5.70 %)	59	54
Other relatives	410	21 (4.87 %)	31	31
Total	1510	75 (4.73 %)	126	293

### *Twin Material*

The twin material comprises all boy twins contacted. Six pairs of twins are contained in the proband material; four pairs were derived from the case records of lying-in Department B, one pair from the University Institute of Human Genetics and one from Surgical Department C of the University Hospital.

In most instances a polysymptomatic similarity test was used to decide the zygosity. This test was in some cases supplemented by blood grouping. In a few instances the diagnosis of monozygosity was based on the appearance of the placenta. In these cases there was one placenta, two membranes in the septum and large superficial vascular anastomoses.

## Chapter 6

### WRITER'S MATERIAL THE PROBAND MATERIAL

The material was divided into the groups listed on p 44 according to the effectiveness of the examination

In addition the families examined were divided according to the severity of the proband's defect The familial cases are illustrated by pedigrees in which the following symbols are used for the males

- ☐ examined genitals normal
- ☐ refused to be examined
- ☐ not examined for some other reason
- ☐ died before the investigation was performed
- ☐ short urethra or low seated orifice
- ☐ juxtaglandular hypospadias
- ☐ penile hypospadias
- ☐ penoscrotal hypospadias
- ☐ perineoscrotal hypospadias
- ☒ more severe malformation of the genitals

In other words each pedigree sets out the result as well as the effectiveness of the examination Families with solitary cases are listed in tables showing the number of relatives of each category who were

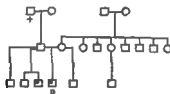
examined and the number of relatives who refused to be examined or who were not examined for some other reason as well as deceased relatives (Tables 10—13) These tables give also the number of sisters and the total number of brothers in the family, the latter in brackets after the number of brothers examined

The classification of the other groups of the material will be seen from the respective tables

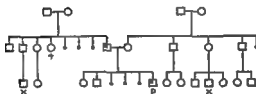
### *I Families examined*

#### *Probands with Juxtaglandular Hypospadias*

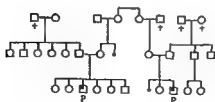
#### *Pedigrees representing families with familial occurrence*



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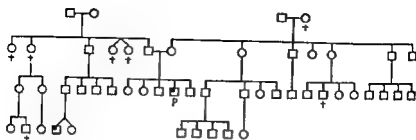


Pedigree 2

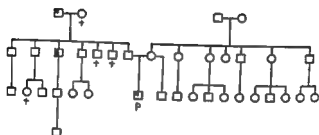


Pedigree 3

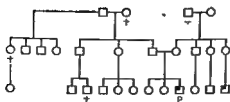
Pedigree 4



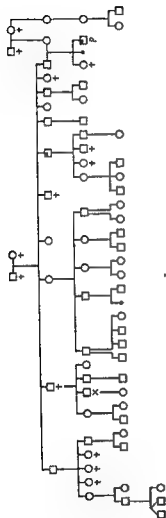
 Pedigree 5



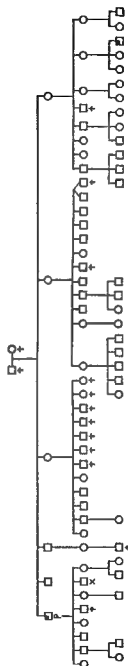
Pedigree 6



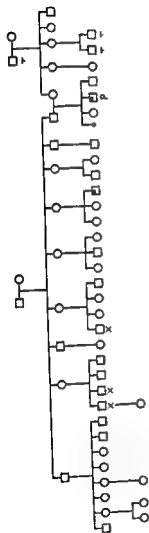
Pedigree 7



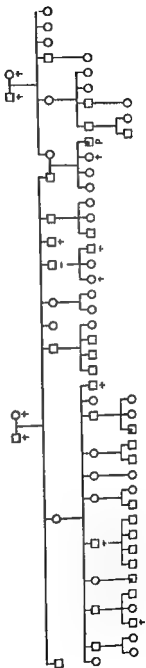
Pedigree 8



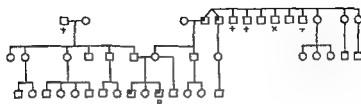
Pedigree 9



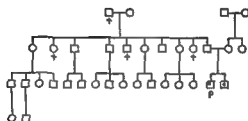
Pedigree 10



Pedigree 11



Pedigree 12



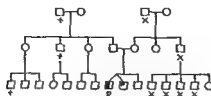
Pedigree 13



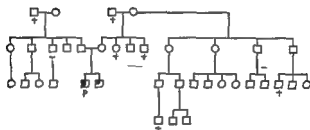
*Table 10*  
Solitary cases of juxtalglandular hypospadias

Patient No	Sisters	Brothers	Fathers	Sons	Grand-fathers	Paternal and maternal uncles	Cousins	Others	Refused to be examined	Others not examined
14	1	2 (2)	1	0	2	4	6	0	0	0
15	0	0 (0)	1	0	1	3	3	0	0	2
16	0	1 (1)	1	0	1	1	2	0	0	3
17	1	1 (1)	1	0	1	1	7	0	2	1
18	1	0 (0)	1	0	1	0	4	0	0	1
19	1	0 (0)	1	0	2	1	2	0	0	0
20	2	1 (1)	1	0	1	4	7	1	0	2
21	1	0 (0)	1	0	1	1	6	0	3	2
22	0	0 (0)	1	0	0	1	1	0	0	5
23	0	1 (1)	1	0	1	0	0	0	0	1
24	0	1 (1)	1	0	2	1	3	0	0	0
25	1	0 (0)	0	0	1	1	0	0	0	2
26	2	0 (0)	1	0	1	4	5	1	0	4
27	1	0 (0)	1	0	1	1	0	0	0	1
28	1	0 (0)	1	0	1	3	6	0	1	2
29	0	0 (0)	1	0	0	0	1	0	0	2
30	0	0 (0)	0	0	2	0	17	4	1	1
31	2	3 (3)	1	0	1	4	10	0	0	0
32	0	2 (2)	1	0	1	3	4	3	0	4
33	1	1 (2)	1	0	2	2	4	0	4	1
34	1	0 (0)	1	0	0	3	2	1	0	3
35	1	2 (2)	1	0	1	1	2	0	0	1
36	1	0 (0)	1	0	0	2	4	0	1	0
37	0	1 (1)	1	0	0	1	5	11	0	4
38	1	0 (0)	1	0	1	2	2	0	0	1
39	2	1 (2)	1	0	1	4	2	6	0	5
40	0	0 (1)	1	0	1	6	10	0	0	10
41	1	0 (1)	1	0	1	12	17	18	0	9
42	2	3 (3)	0	0	0	2	3	5	2	6
43	1	2 (3)	1	0	1	1	4	2	1	5
44	1	1 (2)	1	0	2	3	7	1	0	4
45	0	0 (0)	1	0	1	1	9	13	0	5
46	0	2 (2)	1	0	0	2	6	0	0	2
47	1	1 (1)	1	0	1	1	2	10	0	7
48	4	0 (0)	1	0	1	2	10	0	0	1
49	0	1 (1)	1	0	0	2	2	1	2	0
50	1	1 (1)	1	0	0	4	11	15	3	5
51	1	0 (1)	1	0	0	1	6	14	0	6

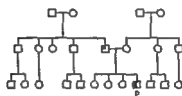
*Probands with Penile Hypospadias*  
*Pedigrees representing families with familial occurrence*



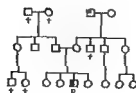
Pedigree 52



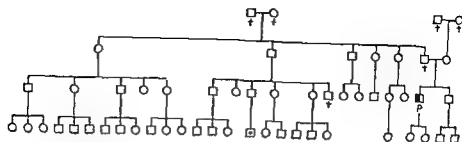
Pedigree 53



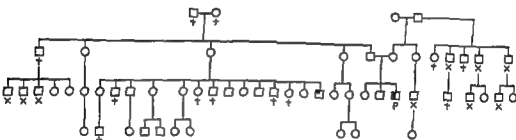
Pedigree 54



Pedigree 55



Pedigree 56

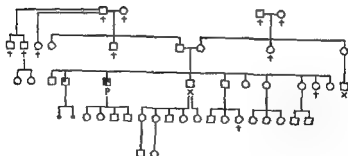
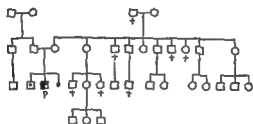
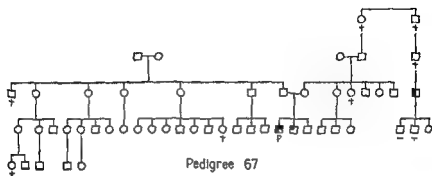


Pedigree 57

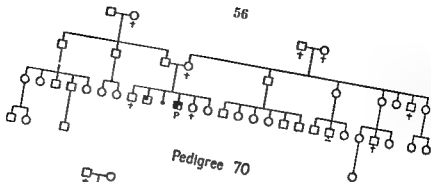
*Table 11*  
Solitary cases of penile hypospadias

Pedigree No	Sisters	Brothers	Fathers	Sons	Grand fathers	Father and maternal uncles	Cousins	Others	Refused to be examined	Others not examined
58	2	0 (0)	1	0	2	3	1	0	11	1
59	2	0 (0)	1	1	1	4	2	0	11	3
60	2	4 (4)	1	0	1	8	8	11	0	1
61	0	1 (1)	1	0	1	1	0	0	0	4
62	11	0 (0)	1	0	1	3	6	11	0	1
63	3	0 (0)	1	0	0	4	1	0	0	5
64	1	0 (0)	1	0	1	3	6	1	0	1
65	1	1 (4)	1	0	1	11	1	11	11	5
66	2	3 (4)	1	1	0	1	1	3	8	3

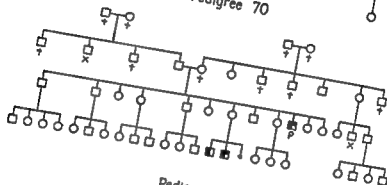
*Probands with Penoscrotal Hypospadias*  
*Pedigrees representing families with familial occurrence*



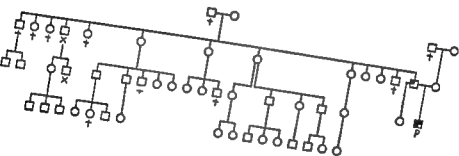
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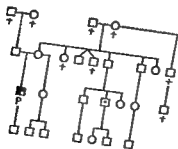
Pedigree 70



Pedigree 71



Pedigree 72

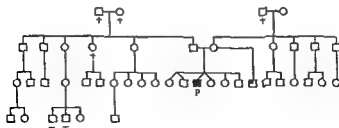


Pedigree 73

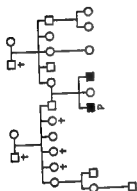
**Table 12**  
**Solitary cases of penoscrotal hypospadias**

Pedigree No	Sisters	Brothers	Fathers	Sons	Grand fathers	Paternal and maternal uncles	Cousins	Others	Refused to be examined	Others not examined
74	1	0 (0)	1	0	0	3	1	1	0	2
75	1	1 (2)	1	0	1	7	4	0	0	2
76	5	1 (1)	1	0	1	2	1	0	0	10
77	0	3 (3)	1	0	1	2	3	0	0	2
78	0	0 (0)	1	0	0	1	4	1	0	2
79	0	0 (0)	1	0	2	7	4	0	0	0
80	2	1 (1)	1	0	0	0	1	5	3	7
81	0	1 (1)	1	0	1	1	1	0	0	1
82	0	0 (0)	1	0	1	1	5	1	0	1
83	2	3 (3)	0	0	1	2	2	2	7	7
84	0	0 (0)	1	0	1	6	23	10	3	8
85	1	0 (0)	1	0	2	0	1	0	0	0
86	3	0 (0)	1	0	0	3	19	6	0	5
87	1	3 (3)	1	0	0	3	14	26	1	7
88	0	1 (1)	1	0	0	0	24	4	0	5
89	0	1 (1)	1	1	0	6	12	16	0	10
90	2	1 (1)	1	0	1	1	3	4	1	1
91	5	0 (0)	1	0	0	5	12	7	0	8
92	1	0 (0)	1	0	1	0	5	2	4	3
93	1	1 (1)	1	0	0	3	12	19	1	8
94	1	0 (0)	0	0	0	1	8	1	0	3
95	2	0 (0)	1	0	1	4	28	26	5	22

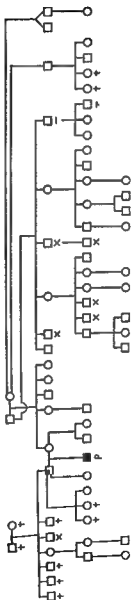
*Probands with Perineoscrotal Hypospadias*  
*Pedigrees representing families with familial occurrence*



Pedigree 96



Pedigree 97



Pedigree 98

*Table 13*  
Solitary cases of perineoscrotal hypospadias

Pedigree No	Sisters	Brothers	Fathers	Sons	Grand fathers	Paternal and maternal uncles	Cousins	Others	Refused to be examined	Others not examined
99	0	II (0)	1	0	1	2	2	0	0	2
100	1	II (0)	1	0	2	4	5	1	0	0
101	2	1 (1)	1	0	2	8	19	0	0	0
102	1	0 (0)	1	II	0	2	10	II	0	7
103	0	0 (0)	1	0	0	0	0	2	II	2

## *II Families Partially Examined*

### *With familial occurrence*



Pedigree 104



Pedigree 105

### *Families without known familial occurrence*

*Table 14*

Number of relatives examined in partially examined families without known familial occurrence

Pedigree Nos	Degree of hypospadias	Fathers	Brothers	Grand fathers	Others
106-122	Juxtaglandular hypospadias	6	8	II	24
123-127	Penile hypospadias	4	II	1	
128-136	Penoscrotal hypospadias	4	5	1	3
137-145	Perineoscrotal hypospadias	4	3		3

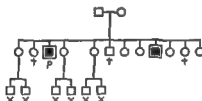


### III. Families Ruled Out

Table 15  
Reason why 27 families were not examined

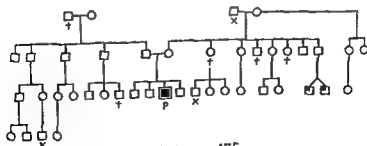
Pedigree No	Degree of hypospadias	Cannot be traced	Foster and adopted children	Refused to be examined
147—157	Juxtaglandular hypospadias	7	3	1
158—159	Penile hypospadias		1	1
160—166	Penoscrotal hypospadias	3	2	2
167—173	Perineoscrotal hypospadias	2	1	4
Total		12	7	8

### IV Families of Interest, but not Belonging to the Material



Pedigree 174

Pseudovaginal hypospadias in two "sisters" (Case report on p 17)



Pedigree 175

True hermaphroditism (case report # 18) and juxtaglandular hypospadias in the same family

## The Twin Material

### *Monozygotic Twins*

#### *Concordant*

(1) Pedigree 52 Aged 10 years Alike physically so as to be mistaken at a distance also by their parents and mentally *Polysymptomatic similarity test* revealed monozygosity Both twins had blood group B *Genitals* I Penile hypospadias II Juxtaglandular hypospadias

(2) Pedigree 12 Aged 54 years I looked so much alike that they were mistaken by their acquaintances Both had operations for right sided inguinal hernia at a few years interval Began wearing spectacles because of farsightedness almost at the same time *Polysymptomatic similarity test* revealed monozygosity Both twins had blood groups A<sub>1</sub> N P C+c D E e+ Le (a) Fy (a+) Kell + *Genitals* Juxtaglandular hypospadias in both

(3) Pedigree 115 Aged 5 years Looked so much alike that they were mistaken by their acquaintances but not by their parents Both weighed 2000 g at birth *Polysymptomatic similarity test* revealed monozygosity Both twins had blood groups O M P+ C+ D+ *Genitals* Juxtaglandular hypospadias in both

(4) University Hospital Lying in Dept B case rec 483/18 I weighed 1800 g and II 2200 g at birth *Placenta* One egg with superficial vascular anastomoses *Genitals* Both infants had slight hypospadias of exactly the same appearance I died a few days after birth

(5) University Institute of Human Genetics Aged 39 years Outward resemblance so striking that they were mistaken by their acquaintances *Polysymptomatic similarity test* revealed monozygosity Both had blood groups O MN P+ C $\bar{c}$ +D E e+ Le (+) Fy (a) Kell *Genitals* Examination of the penis showed in both twins the scar of a successful correction of hypospadias by the method of Beck By the appearance of the scar the defect must have been of the juxtaglandular variety in both cases

#### *Discordant*

(6) Pedigree 95 Aged 26 years Outward resemblance so striking that they were mistaken by acquaintances *Polysymptomatic similarity test* revealed monozygosity Both had blood groups O MN P+ C+c+D+E Le (a) I $\bar{a}$  (b+) *Genitals* I Penoscrotal hypospadias II Normal genitals

(7) Lying in Dept B Rigshospitalet Copenhagen case rec 391/50  
Birth weights I 3550 g II 2350 g *Placenta* One large placenta septum  
with two membranes superficial anastomoses between the two halves  
Both had *blood groups* A<sub>1</sub> P C+ $\bar{c}$ +D+I  $\bar{c}$ + Le (a) *Genitals* I Normal  
II Juxtaglandular hypospadias

(8) Lying in Dept B Rigshospitalet Copenhagen case rec 1514/51  
Birth weights I 1900 g II 900 g No information regarding the placenta  
(the delivery took place at home) *Polysymptomatic similarity test*  
(at the age of 2½ months) revealed exactly the same eyes and ears  
Both had *blood groups* O N P+ C+D+I + I e (r+) I u (a) Fy (r+)  
*Genitals* I Normal II Penoscrotal hypospadias

(9) University Hospital Surgical Dept C case rec 702/52 Aged 15  
years Birth weights I 3100 g II 3350 g *Placenta* Septum with two  
membranes Outward resemblance so striking that they were mistaken  
by their acquaintances *Polysymptomatic similarity test* revealed mono-  
zygosity Both had *blood groups* A<sub>1</sub> M P+ C+ $\bar{c}$ + D+I e+ I<sub>1</sub> (a+) Fy  
(a+) *Genitals* I Scar following operation for penoscrotal hypospadias  
by the method of Dennis Browne II Normal

### *Dizygotic Twins*

#### *Discordant*

(10) Pedigree 31 Aged 12 years Are never mistaken for each other  
*Polysymptomatic similarity test* revealed dizygosity Both have *blood*  
*group* O *Genitals* I Normal II Juxtaglandular hypospadias

(11) Pedigree 32 Aged 6 years Are never mistaken for each other  
Birth weights I 2750 g II 2600 g *Polysymptomatic similarity test*  
revealed dizygosity *Genitals* I Normal II Juxtaglandular hypospadias

#### *A pair of twins whose zygosity was not ascertained*

(12) Lying in Dept B Rigshospitalet Copenhagen case rec 384/38  
Birth weights I 1950 g II 1000 g *Placenta* Two completely separated  
placentae with a septum of four membranes *Genitals* II Hypospadias  
Died four days post partum

## Chapter 7

### EVALUATION OF WRITER'S MATERIAL

#### *Uniformity*

In this material the diagnosis of hypospadias had been made by clinical examination. As mentioned above, therefore some erroneous diagnoses cannot be ruled out among the cases combined with cryptorchidism, as the gonads were not always examined in exploratory laparotomy.

Although a natural grading is impossible, it would be interesting to investigate whether aetiological differences appear to exist between the different degrees set up artificially considering the marked morphological differences between mild and severe cases. From the genetic point of view, it must be ascertained, whether familial occurrence is met with in all degrees and whether intrafamilial variations occur.

Table 16 gives the incidence of familial cases classified according to the severity of the proband's defect. It is evident that familial cases were encountered in an average of 28.1 % of the families. When considering that the numbers involved are small, we find no difference in the incidence of the different degrees.

Studying the individual families with familial occurrence (including 104 and 105) with a view to intrafamilial variation, we find the same

Table 16

Incidence of familial cases grouped according to the severity of the proband's defect

Juxtaglandular cases	13	familial out of 51 (25.5 %)
Penile cases	6	" " " 15 (40.0 %)
Penoscrotal cases	7	" " " 29 (24.1 %)
Perineoscrotal cases	3	" " " 8 (37.5 %)
Total cases	29	familial out of 103 (28.1 %)

(7) Iying in Dept B Rigshospitalet Copenhagen case rec 391/50  
Birth weights I 3550 g II 2350 g *Placenta* One large placenta septum  
with two membranes superficial anastomoses between the two halves  
Both had *blood groups* A<sub>1</sub> P C+ $\bar{c}$ +D+I  $\bar{e}$ + I e (1) *Genitals* I Nor  
mal II Juxtaglandular hypospadias

(8) Iying in Dept B Rigshospitalet Copenhagen case rec 1514/51  
Birth weights I 1900 g II 900 g No information regarding the pla  
centa (the delivery took place at home) *Polysymptomatic similarity*  
*test* (at the age of 2½ months) revealed exactly the same eyes and ears  
Both had *blood groups* O N P+ C+D+I + I e (1+) I u (a) Fy (a+)  
*Genitals* I Normal II Penoscrotal hypospadias

(9) University Hospital Surgical Dept C case rec 702/52 Aged 15  
years Birth weights I 3100 g II 3300 g *Placenta* Septum with two  
membranes Outward resemblance so striking that they were mistaken  
by their acquaintances *Polysymptomatic similarity test* revealed mono  
zygosity Both had *blood groups* A<sub>1</sub> M P+ C+ $\bar{c}$ + D+I  $\bar{e}$ + I e (a+) Fy  
(a+) *Genitals* I Scar following operation for penoscrotal hypospadias  
by the method of Dennis Browne II Normal

### *Dizygotic Twins* *Discordant*

(10) Pedigree 31 Aged 12 years Are never mistaken for each other  
*Polysymptomatic similarity test* revealed dizygosity Both have *blood*  
*group* O *Genitals* I Normal II Juxtaglandular hypospadias

(11) Pedigree 32 Aged 6 years Are never mistaken for each other  
Birth weights I 2750 g II 2600 ■ *Polysymptomatic similarity test*  
revealed dizygosity *Genitals* I Normal II Juxtaglandular hypospa  
dias

### *A pair of twins whose zygosity was not ascertained*

(12) Iying in Dept B Rigshospitalet Copenhagen case rec 384/38  
Birth weights I 1900 g II 1000 g *Placenta* Two completely separated  
placentae with a septum of four membranes *Genitals* II Hypospadias  
Died four days post partum



type in 14 families and a variation in the severity in 17 (cf Table 17). The variation may be so marked that the very mildest and the most severe cases occur in the same family.

Since no difference is demonstrable in the incidence of the familial occurrence of the different degrees of the lesion and since marked intrafamilial variation in degree may be encountered the aggregate material will be considered as one in studying the etiological significance of heredity.

*Table 17*

Degree of hypospadias in the malformed individuals within the same family  
Same degree in 14 families

Juxtaglandular hypospadias 4 cases in 1 family

Juxtaglandular hypospadias 2 cases in 10 families

Penoscrotal hypospadias 2 cases in 2 families

Perineoscrotal hypospadias 2 cases in 1 family

Varying degree in 17 families

Low seated orifice and juxtaglandular hypospadias in 1 family

Low seated orifice and penile hypospadias in 1 family

Low seated orifice and penoscrotal hypospadias in 2 families

Juxtaglandular and penile hypospadias in 5 families

Juxtaglandular and penoscrotal hypospadias in 3 families

Juxtaglandular and perineoscrotal hypospadias in 2 families

Juxtaglandular — 2 cases — and penile hypospadias in 1 family

Juxtaglandular penile and penoscrotal hypospadias in 1 family

Penile hypospadias and 2 cases of penoscrotal hypospadias in 1 family

### *Incidence of the Defect Among the Probands' Relatives*

A total of 1590 relatives were examined. Twenty eight had hypospadias and four well defined short urethra or low seated orifice. In other words the incidence among the probands' relatives is 1.76 % which is statistically higher — at the 1 % significance level — than that among the total male population which was 0.33 %. Thus the standard error of the difference equals 0.52 % according to the formula

$$\sqrt{P(1-P) \times \left( \frac{1}{n_1} + \frac{1}{n_2} \right)}$$

(Kemp 1942 p. 99) and 1.76 % — 0.33 % = 1.43 % > 2.58 × 0.52 % = 1.34 %. The 75 relatives who refused to be examined give rise to an uncertainty but even though they are counted as normal the difference between the two groups is definite at the 1 % significance level since the standard error of the difference equals 0.51 % and 1.68 % — 0.33 % = 1.35 % > 2.58 × 0.51 % = 1.32 %.

Table 18

Incidence of hypospadias among the various categories of relatives.

	With hypospadias	Without hypospadias	%, with hypospadias
Brothers	10	94	9.6
Half-brothers	2	25	7.4
Fathers	4	111	3.5
Sons	0	17	0.0
Grandfathers	1	79	1.3
Paternal or maternal uncles	2	277	0.7
Nephews	2	58	3.3
Cousins	4	560	0.7
Others	11	317	1.5
Total	32	1558	2.0

The incidence in the various groups of relatives will be seen from Table 18. This table includes the 4 cases of low-seated orifice and short urethra, all of which occurred among the close relatives.

#### *Concordance and Discordance among Twins*

In Table 19 *Lamy's* (1952) twin material is compared with the present material of twins.

Table 19

Concordance and discordance among mono- and dizygotic twins

	Monozygotic twins		Dizygotic twins	
	Con- cordance	Dis- cordance	Con- cordance	Dis- cordance
<i>Lamy's series</i>	3	3	0	4
<i>Writer's series</i>	5	4	11	2
	8	7	0	11

The  $\chi^2$  test, using Yates' correction (*Kemp* (1942), p. 128), shows a tendency that concordance is more common among monozygotic than among dizygotic twins ( $\chi^2 = 3.15$ ,  $f = 1$ ,  $p = 0.07$ ).

#### *Heredity*

Since hypospadias occurs with an increased incidence among the relatives of hypospadians and since concordance appears to be more



common among monozygotic than dizygotic twins, it must be inferred that the lesion is dependent on inherited factors

Although hypospadias occurs only in men, the gene may be transmitted by women (Pedigrees 3, 4, 7, 9, 10, 11, 12, 55, 57, 67, 71, 73, and 96) as well as by normal (Pedigrees 1, 5, 6, 8, 10, 11, 56, 57, and 73) and afflicted men (Pedigrees 2, 6, 12, 54, 55, 72, and 98)

As mentioned above, the lesion must depend on exogenous factors, as only 8 out of 15 pairs of monozygotic twins showed concordance. At 2.58 times the standard deviation — 99 % probability level — this means that concordance must exist in between 36.6 and 87.5 % of the monozygotic twins. This corresponds to a degree of manifestation somewhere between 54 and 93 % (cf Kemp (1943) p 117—118). A similar degree of manifestation must be present in the proband material. The mode of inheritance may, thus, be indicated by the degree of manifestation, since the numbers involved are too small to be treated by the usual statistical methods. Table 20 lists the actual and expected number of cases occurring in some categories of relatives at dominant and recessive heredity respectively. The expected number was calculated on the basis of Dahlberg & Hultkrantz' formulas (Kemp (1943) p 112—113). The actual number is  $19 \pm 2.58 \times 4.36$ , while the expected number was 225.1 at pure Mendelian dominance. At a probability level of 99 %, therefore, the degree of manifestation must be between 3.4 and 13.5 % providing dominant heredity with failing manifestation. These values do not accord with the degree of manifestation calculated on the basis of the twin material, and this mode of inheritance is, therefore, unlikely. In recessive heredity the expected number of cases is 50.3, corresponding to a degree of manifestation between 15.4 and 60.1 % with a probability of 99 %. In recessive heredity with failing manifestation, thus, the degree of manifestation accords rather well with that in the twin material and the proband series. Table 20 shows, moreover, a rather constant ratio between the actual number and that expected in the various categories of relatives, provided that the heredity is recessive. This calculation, however, has the drawback of not holding good, if too many of the cases depend exclusively on exogenous factors. In practice, however, it may be expected that in a large series the cases are distributed as a lesion transmitted by recessive heredity with failing manifestation.

Although the high incidence of hypospadias means that the gene of this lesion must be commonly present among the population, it must probably be assumed that the frequency of consanguinity is increased if hypospadias is a recessive character. In 124 families, three cases of consanguinity occurred among the probands' parents. This exceeds the

Table 20

*Number of hypospadias in various categories of relatives compared with the number expected at dominant and at recessive heredity*

	Total number of relatives	Dominant		Actual number	Recessive	
		Expected % affected	Expected number affected		Expected % affected	Expected number affected
Children	17	50.13	8.5	0	5.72	1.0
Brothers	104	50.11	52.1	10	27.80	28.9
Grandfathers	367	25.21	92.5	5	3.01	11.0
Grandchildren						
Paternal and maternal uncles						
Cousins	565	12.75	72.0	4	1.67	9.4
Greatgrandfathers						
Total	1053		225.1	19		50.3

ordinary incidence of consanguinity in Denmark, which is believed to be lower than 1 %. Owing to the small numbers involved, however, this finding cannot be attributed with much significance.

It may be concluded that hypospadias is dependent on exogenous as well as endogenous factors. The latter are probably transmitted as recessive characters.

## Chapter 8

### RELATION OF HYPOSPADIAS TO SOME INTERSEXUALITY THEORIES

An intersex is defined by *Goldschmidt* (1915) as an individual developing against its genetic sex. According to the original sex, a distinction is made between male and female intersexes. A distinction is made also (1931) between zygotic intersexuality in which the sex inversion takes place at the moment of fertilization, and hormonal intersexuality induced by the hormones of the opposite sex.

#### *Goldschmidt's Intersexuality Theory* (Zygotic Intersexuality)

Goldschmidt's intersexuality theory is briefly as follows:

In male as well as female individuals the chromosomes contain both masculine and feminine sex determining factors. These factors are inherited and may be of varying strength. Weak and strong factors may be combined in a way so as to give rise to a divergence from normal in the ratio masculine and feminine factors, and an intersexual individual results. For instance, the combination of strong masculinizing and feminizing factors in a genetically female individual results in a female intersex. The mechanism of the development of intersex is explained as follows. During early foetal life, the individual develops according to its original sex, but at some juncture, the turning point, the factors of the opposite sex prevail and after that time, the development takes the opposite direction. If the preponderance of the opposite sex is very strong the turning point occurs at an early stage of foetal life and the individual develops markedly against its genetic sex.

*Goldschmidt* (1911, 1915, 1931, 1933) proved his theory on the moth *Lymantria* in innumerable crossing experiments between various geographic varieties, the sex-determining factors of which were of varying strength. By applying this theory to normal embryology and the mor-

phology of genital malformations *Goldschmidt* (1931) explained a large number of malformations in animals and man

As far as the human race is concerned the female is supposed to possess two feminizing and two masculinizing factors and the male one feminizing and two masculinizing factors In man only female intersexuality is said to occur Severe cases of hypospadias are regarded as female intersexes while the milder ones are interpreted as anomalies of developmental arrest as patients with mild hypospadias have had normal sons According to this theory female intersexes — who thus possess two X chromosomes — can have only daughters or intersexual children *Berblinger* (1936) shares *Goldschmidt's* view while *Moszkowicz* (1936) has gone even further interpreting also mild cases of hypospadias retention of the testes and homosexuality as intersexual phenomena On the basis of embryologic studies on the development of the masculine and the feminine prepuce *Popper* (1937) states that the prepuce of hypospadias is feminine and he therefore subscribes to *Moszkowicz's* ideas

### Writer's Investigations

In order to assess the validity of the intersexuality theory in hypospadias the writer employed the methods used by *Goldschmidt* in studying the *Gymnuris*

- (1) Sex distribution among the offspring
- (2) Sex distribution in the siblings
- (3) Occurrence of sex linked recessive characters in intersexes and their parents

### Sex Distribution Among the Offspring of Hypospadias

The series counts a total of 68 persons with hypospadiac fathers Table 21 gives the sex distribution of these persons classified according

Table 21

The sex distribution among the children of hypospadias shows no divergence from normal

	Cases	Boys			
		Total	With hyposp.	Normal	Intersexual
Sublingual or hypospadias	20	27	3	17	7
Penile hypospadias	5	5		3	2
Penoscrotal hypospadias	5	11		4	7
Total	30	43	3	24	16

Table 22

Distribution of male and female individuals in the sibships, when *juxtaglandular cases* are interpreted partly as male, partly as female. Good conformity with the expected number will be seen in the former, lacking conformity in the latter case.

Sibship		Hypospadias				Number of sibships × σ <sup>2</sup>
Size of	Number of	Interpreted as males		Interpreted as females		
		Expected number of males	Actual number of males	Expected number of females	Actual number of females	
2	23	30.667	31	30.667	39	5.106
3	15	25.710	31	25.710	30	7.350
4	9	19.197	23	19.197	22	7.038
5	6	15.486	16	15.486	20	6.492
6	4	12.192	13	12.192	15	5.516
10	1	5.005	4	5.005	7	2.478
11	1	5.503	6	5.503	6	2.737
59		113.760	124	113.760	139	36.717
		124 ± 6.06 × 3		139 ± 6.06 × 3		

Table 23

Distribution of male and female individuals in the sibships, compared with the expected number, when *penile hypospadians* are interpreted in part as genetically male, in part as genetically female. A better conformity is found, when the patients are interpreted as male.

Sibship		Hypospidius				Number of sibships $\times \sigma^2$
		Interpreted as males		Interpreted as females		
		Expected number of males	Actual number of males	Expected number of females	Actual number of females	
2	7	9.333	12	9.333	10	1.554
3	3	5.142	4	5.142	8	1.470
4	5	10.665	7	10.665	18	3.910
5	1	3.048	5	3.048	2	1.379
7	2	7.056	10	7.056	6	3.334
18		35.244	48	35.244	44	11.647
			$38 \pm 3 \times 3.41$		$44 \pm 3 \times 3.41$	

Table 24

Distribution of male and female individuals in sibships, when *penoscrotal* cases are interpreted partly as male, partly as female individuals. Good conformity with the expected number in the former, lacking conformity in the latter case.

Sibship		Hypospadians				Number of sibships $\times \sigma^2$
Size of	Number of	Interpreted as males		Interpreted as females		
		Expected number of males	Actual number of males	Expected number of females	Actual number of females	
2	12	16 000	16	16 000	22	2 664
3	6	10 284	11	10 284	14	2 940
4	7	14 931	17	14 931	19	5 474
5	2	5 162	7	5 162	6	2 104
6	2	6 096	7	6 096	11	2 758
7	1	3 528	2	3 528	6	1 667
8	1	4 016	5	4 016	4	1 945
10	1	5 005	5	5 005	7	2 478
12	1	6 001	5	6 001	7	2 992
33		71 023	75	71 023	94	25 082
			$75 \pm 3 \times 5.00$		$94 \pm 3 \times 5.00$	

Table 25

Distribution of male and female individuals in the sibships, when *perineo scrotal* cases are interpreted partly as male and partly as females individuals. Good conformity with the expected number in the former, lacking conformity in the latter case.

Sibship		Hypospadians				Number of sibships $\times \sigma^2$
Size of	Number of	Interpreted as males		Interpreted as females		
		Expected number of males	Actual number of males	Expected number of females	Actual number of females	
2	6	8 000	10	8 000	8	1 332
3	3	5 142	5	5 142	8	1 470
4	2	4 266	3	4 266	7	1 564
■	1	2 581	2	2 581	1	1 082
■	1	3 048	3	3 048	4	1 379
11	1	5 503	3	5 503	11	2 478
		28 540	26	28 540	40	11 305
			$26 \pm 3 \times 3.05$		$40 \pm 3 \times 3.05$	

to the degree of the father's malformation. This table shows also how many of the boys had been examined and how many were normal.

All degrees of hypospadias, apart from perineoscrotal cases, are represented. There were normal boys in all groups, and the sex distribution did not differ from normal.

### *Sex Distribution in Sibships Including Hypospadias*

For each of the four varieties of hypospadias I calculated the expected number of male and female individuals among the patients' siblings, in part when the patients are interpreted as genetically male and in part when they are interpreted as genetically female. This calculation was carried out by means of Koller's tables (Koller (1940)). The results are presented in Tables 22-25 with the actual number and the calculated standard deviation.

In juxtaglandular, penoscrotal and perineoscrotal cases there is a statistically significant difference between the expected and actual number of females, when the hypospadias are interpreted as genetically female while good conformity is seen, when they are interpreted as genetically male. In the penile cases, the numbers involved are too small to permit a statistical evaluation. Even so, the results accord better when the hypospadias are considered genetically male.

### *Occurrence of Sex-linked Recessive Characters in Hypospadias*

Colour blindness is a common, recessive, sex-linked character in man. Determined by the Ishihara test, it is said to occur in about 8 % of all males and in about 0.5 % of all females (Waaler (1927)). Therefore, a large number of the probands and their parents were examined for colour blindness by means of Ishihara's plates (1936) in an endeavour to determine the genetic sex of the hypospadias.

The result is set out in Table 26. Colour blindness occurred in all

Table 26

Distribution of colour blindness among the hypospadias, their normal fathers and mothers

	Probands		Fathers		Mothers	
	Total	Colour blind	Total	Colour blind	Total	Colour blind
Juxtaglandular hypospadias	56	3	42	7	42	0
Penile hypospadias	10	1	11	1	12	0
Penoscrotal hypospadias	28	■	22	0	22	0
Perineoscrotal hypospadias	10	1	4	1	7	■
Total	104	7	79	9	83	0

degrees of hypospadias. When regard is paid to the small numbers involved there does not appear to be any difference in the incidence among the hypospadias and their fathers. Moreover the incidence — 6.73 ( $p_m$  in % is 18.03 and  $p_m$  in % 2.31) — does not differ from that applying to normal males. On the other hand it is too high for genetically female individuals.

If a colour blind hypospadias is interpreted as genetically female it must also be demanded — on account of the mode of inheritance of recessive sex linked characters — that the father is colour blind provided that he cannot be interpreted as intersexual due to a genital malformation. In this series two colour blind patients with juxtaglandular and one with penile hypospadias had fathers with normal colour vision and normal genitals. One colour blind patient with perineoscrotal hypospadias had a father with a normal colour vision but with juxtaglandular hypospadias. In the last case both juxtaglandular and perineoscrotal cases of hypospadias would have to be interpreted as intersexes if the child with perineoscrotal hypospadias is to be interpreted as such. The fathers of the remaining colour blind hypospadias had died but as far as was known they had had normal colour vision and normal genitalia.

Therefore neither the sex distribution found among the children and the siblings of the hypospadias nor the incidence of the sex linked recessive character colour blindness indicate that hypospadias mild or severe — should be on the whole interpretable as genetically intersexual.

### *Hormonal Intersexuality*

It has been shown repeatedly in animal experiments that the normal development of the foetal genitals may be changed by the administration of sex hormones to the mother (cf. Dantchakoff (1938), Greene (1942, 1944), Moore (1944)). This even applies to species as superior as monkeys (van Wagenen & Hamilton (1943)). These experiments were carried out to elucidate the mechanism of the normal development of the genitals but they have also given rise to speculations regarding the aetiology and pathogenesis of genital malformations. Various authors have tried to relate the aetiology of the malformations to their theories regarding the normal sex differentiation. In addition to the gonads it has been suggested that the adrenals might be of significance in sex differentiation and development of intersexuality (Broster (1947)).

Despite marked divergences between the different views regarding the significance of hormones and their mode of action in the develop-



## Chapter 2

### EXOGENOUS AETIOLOGICAL FACTORS

Recently, it has been realized that malformations may be the result of foetal infection with rubella (cf *Albaugh (1943)* *Bardram & Brandstrup (1947)*). Such malformations are mainly localized to the eyes, heart and brain but a few cases of hypospadias have been reported following maternal rubella during pregnancy (*Prendergast (1946)*, *Keizer (1950)*). When considering the high incidence of hypospadias, however these may have been chance coincidences.

Also animal experiments have shown that exogenous factors may, via the maternal organism, cause malformation of a foetus. If pregnant experimental animals are exposed to vitamin deficiency, part of the litter will be born with malformations. The nature of such malformations depends on which vitamin is withdrawn from the diet (*Warkany (1948)*). Avitaminosis A has been followed by intestinal genital malformations (*Bendixen (1944)*). Even a quite brief oxygen deficiency may cause malformations. *Ingalls, Curley & Prindle (1950)* exposed pregnant mice to anoxia. Among their offspring congenital defects were far more common than in a control series. Malformations have also been induced by treating pregnant mice with cortisone. This resulted initially in harelip in the offspring (*Fraser & Fainstat (1951)*). The number of mice with harelip proved to depend upon which strain was used in the experiment. In other words, there must have been a certain interplay between genetic factors and the exogenous action of the cortisone. Toxic damage of the spermatozoon may also be mentioned among the causes of experimental malformations. Artificial insemination with spermatozoa treated with colchicine in low concentrations has resulted in offspring with a high incidence of spina bifida (*Nachtsheim (1951)*).

The nature of the malformation depends on the stage of foetal life at which the exogenous factor is active. According to *Ingalls* experiments (1930) rapidly growing tissues sustained most damage. In the case of rubella also the malformation depends on the time of the deleterious action (*Dods* (1948)). Moreover combined malformations may occur in tissues of the same embryological age (*Ipsen jr & Okl els* (1932) *Grunfelder & Lasch* (1949)).

As far as human malformations are concerned it is difficult to elucidate the nature of the exogenous factors. It is impossible to procure a suitable material. Birth records have the advantage that the history has been taken at the termination of pregnancy but the drawback that it has not been taken with a view to the aetiology of malformations. This is obtained by taking the data from the parents of malformed children but in such cases many years may have passed from the pregnancy concerned so that presumably the data are not quite reliable.

### *Writer's Investigations*

Despite some scepticism regarding the possibility of demonstrating exogenous factors the writer perused the 90 records from Lying in Department B with such factors in mind. Furthermore I interviewed the mothers of 34 hypospadias regarding the course of the pregnancy.

If an exogenous factor is to be attributed with any significance it must have been active before the development of the urethra has been completed i.e. before the end of the fourth month of gestation (*Spanthling* (1921)). For this reason I looked only for abnormalities during the first four months of gestation.

This material was perused with a view to

*Infectious diseases* which were not reported in any case.

*Avitaminoses* of which I found no evidence. Also there was no case of hyperemesis which might be imagined to cause vitamin deficiency.

*Somatic and psychic trauma*. No well defined cases.

*Hæmorrhages*. During the first four months there were 7 cases of hæmorrhage among 124 patients. The hæmorrhage was however mild in all cases and the incidence is not high enough to be attributed with any significance.

*Intoxications*. The parents of a perineo-ovular hypospadias reported that they had both been under the influence of alcohol when the child was conceived.

It will be seen that the present series permits no conclusions regarding the nature of the exogenous factors. As mentioned above however the series was not particularly suitable for this purpose and despite

the negative findings, some of the factors mentioned may have been operative

Seeing that infectious diseases are subject to seasonal variations, a seasonal variation in the incidence of hypospadias in the newborn might be expected if infection is an aetiological factor. Such a variation might also be imagined to be caused by a possible aetiological vitamin deficiency, as the supply of vitamins is at a minimum during the spring

Therefore, the birth dates of the 262 hypospadias are presented in Table 29 compared with the expected number, calculated on the basis of the birth dates of boys born in 1944 (Statistique du Danemark, 1945). The difference between the actual and expected number is seen to be quite irregularly distributed on the 12 months of the year. The  $\chi^2$  test shows no significant difference between the actual and expected number of cases ( $F = 11$ ,  $\chi^2 = 11.08$ ,  $0.5 > p > 0.4$ )

Among the twin material there are 5 discordant cases in which the birth weight is known. In all these cases, the malformed twin had the lowest birth weight or 47.3, 51.2, 66.2, 92.5, and 94.6 % respectively of the healthy twin's weight.

Table 29

262 cases of hypospadias classified according to the month of birth compared with the expected number born in each month. No seasonal variation

	Number of boys born in 1944	Cases of hypospadias		$n - x$	$\frac{(n - x)^2}{n}$
		Expected $n$	Actual $x$		
January	3,896	21.32	30	- 8.68	3.5338
February	3,884	21.25	19	+ 2.25	0.2382
March	4,379	23.96	30	- 6.04	1.5226
April	4,195	22.95	19	+ 3.95	0.6798
May	4,142	22.67	17	+ 5.67	1.4181
June	3,915	21.42	25	- 3.58	0.5983
July	4,026	22.03	17	+ 5.03	1.1484
August	3,946	21.59	25	- 3.41	0.5385
September	3,924	21.47	23	- 1.53	0.1090
October	3,850	21.07	22	- 0.93	0.0410
November	3,790	20.74	17	+ 3.74	0.6744
December	3,934	21.53	18	+ 3.53	0.5787
	47,881	262.00	262		11.0808

Occasioned by this finding, the writer studied the birth weight of 90 hypospadias born in Lyngby Department B compared with that of all boys discharged alive every fifth year during the same period. These

values are set out in Table 30. True, this table shows a higher incidence than expected in the low and a lower incidence in the high weight groups, but the difference is not statistical ( $\chi^2 = 7.973$ ,  $p = 0.1$ ).

Table 30

Birth weight of 90 hypospadias compared with that of 5493 normal boys discharged alive. No statistical difference.

Birth weight	Control series number	Hypospadias		$\frac{(a-x)^2}{a}$
		Expected number	Actual number	
Under 2500 g	512	8.2	11	0.8689
2550—2750 g	449	7.2	7	0.0066
2800—3000 g	704	11.3	14	0.6287
3050—3250 g	990	15.9	19	0.5916
3300—3500 g	1076	17.3	22	1.2670
3550—3750 g	870	14.0	9	1.7881
3800—4000 g	565	9.1	3	4.0800
over 4000 g	427	6.9	5	0.5076
	5593	90.0	90	9.7381

### Combination with Other Malformations

Other congenital defects occurred in 9 of the 173 probands, viz. three with juxtaglandular, two with penile, one with penoscrotal and three with perineoscrotal hypospadias.

On the basis of the small numbers involved it is impossible to state whether the incidence of other malformations is increased in hypospadias. If such a combination is to be explained on the basis of a common aetiological factor, the development of the affected organs must take place at the same foetal stage as that of the urethra, which is completed in the fourth month of gestation.

The other congenital defects were as follows.

**Hardness of hearing** due to a perceptive defect in three patients with juxtaglandular, penile and penoscrotal hypospadias respectively. The degree of hypospadias and deafness was proportional. As the inner ear has practically reached its definite form in the 8th foetal week (Grey (1942) p. 496) the juncture corresponds fairly well with that of the urethral development.

**Harelip and cleft palate** in two cases, one of juxtaglandular and one of perineoscrotal hypospadias. The union of the two halves of the palate usually takes place in the 9th foetal week (Grey (1942) p. 198).

This defect therefore may also be related chronologically to hypospadias

*Megacolon and anal stricture* in one case of familial juxtaglandular hypospadias. Owing to the close relation between the development of the rectum and the urogenital organs it is natural to relate these two malformations to each other

*Clubfoot* in the first mentioned patient and in one with perineoscrotal hypospadias. In the latter case clubfoot as well as hypospadias were familial. It is impossible to state whether clubfoot and hypospadias may be related etiologically. True the development of the limbs sets in at a very early stage but that of the skeleton of the foot ranges over a very long period

*Feeble-mindedness* in two cases. A patient with penile hypospadias suffered from mild feeble-mindedness which occurred also among other members of the otherwise intelligent family. The other patient with perineoscrotal hypospadias was an imbecile. This patient also had Little's disease. Therefore it cannot be ruled out that the feeble-mindedness may have been due to birth injury

A number of the congenital defects encountered in the hypospadias may be explained as developmental arrest due to one or more inhibitory factors which at the same time have arrested the development of the genitals. The aetiological factors may also be imagined to have given rise to a generalized inhibition of growth. At least this would explain why the hypospadian among a pair of discordant twins is invariably the smaller one. These presumptions however do not receive sufficient support from the present material

## *Chapter 10*

### CONCLUSION AND DISCUSSION OF THE PRACTICAL SIGNIFICANCE OF THE RESULTS

Although the etiology of hypospadias has not been fully elucidated the results of the present study are of practical significance from the point of view of eugenics as well as operative criteria

Before discussing these aspects the author would like to give a brief summary of the results

#### *Conclusion*

Hypospadias is a congenital defect occurring in about 0.33 % of the male population. There are mild and severe cases with even transitions. The foreskin and urethra are invariably deformed, but the other external as well as the internal genitals may also be involved. For example retention of the testes is a common associated phenomenon. Hypospadians marry as often as do normal men. In mild cases their sexual relations are normal, whereas in severe cases surgical correction of the penile flexion is required. The fertility is normal in mild cases, decreasing with increasing severity of the defect. The lesion is familial in about one-quarter of all cases, and within the same family there may be wide variations in degree. As far as the etiology is concerned, both endogenous — inherited — and unknown exogenous factors must be considered. The mode of inheritance appears to be recessive with failing manifestation. The patients' genetic sex is male. They cannot be interpreted as intersexes according to Goldschmidt's theory.

#### *Eugenic Measures*

In Denmark it is permitted to interrupt a pregnancy when there is a risk that the child will be affected with a serious, incurable inherited

disease. The criteria must, thus, be based on the risk as well as on the more or less serious nature of the disease.

Since the heredity of hypospadias appears to be recessive with failing manifestation, the risk of familial cases is slight. It is highest for the brothers of a hypospadian, but at the mode of inheritance mentioned, it does not by any means reach 25 %. In other words, if a couple have had one child with hypospadias, the risk that their next child will be affected has been reduced to considerably less than 12.5 %, as the ratio boys/girls in these sibships does not differ from normal. The next highest risk will be found in the group sons of hypospadians. In this group, however, the risk is far lower than among the brothers.

But regard must be paid also to the nature of the lesion. The fact is that only about 25 % of the patients have complaints necessitating surgical correction. The latter has caused some difficulty in the course of time, but recently good results have been obtained, also in Denmark (*Fogh-Andersen (1953)*).

Hypospadias, therefore, is probably not an indication for interruption not even in the most severe cases. Owing to the intrafamilial variation, it is impossible to tell how severe the next case in the family will be.

In the general run of eugenic consultation, there is probably no reason to advise against having children or against marriage between first cousins, even though the male partner is affected with hypospadias.

Since about three-quarters of the patients have shown normal fertility and since there is intrafamilial variation in the severity, the absence of eugenic measures will probably not have much influence on the incidence of the defect or on the distribution of mild and severe cases.

### *Operative Indications*

According to these eugenic considerations, there is hardly any reason to deprive hypospadians of the pleasure of having children. Therefore, the possibility of improving a reduced fertility must be taken into consideration in setting up the operative indications.

Juxtaglandular cases require no treatment apart from dilatation and perhaps meatotomy of a constricted orifice. The difficulty of micturition is slight and fertility as well as sexual function normal. Penile hypospadias is a transitional variety, in each individual case the advisability of surgical treatment must be considered. In more severe cases, the flexion of the penis has to be straightened to render sexual functions

normal, and reconstruction of the urethra is required to obviate difficulties of micturition and improve the fertility.

In other words, three-quarters of all cases require no treatment. The new surgical procedures for juxtaglandular hypospadias which are still being worked out (*Nahoum* (1947), *Brendler* (1948)) must be taken as contributions to cosmetic surgery. The treatment of the last one-quarter demands experience and care. It is therefore worth considering whether the approximately 30 new cases annually should not be centralized in a few departments.



## SUMMARY

### *Introduction*

The main object of the present study was to elucidate the aetiology of hypospadias

### *Chapter 1*

Reviewing the morphological features of the disease the writer finds an even transition between the mild and severe degrees. For the purposes of the present work it is most practical to subdivide the condition into juxtaglandular penile penoscrotal and perineoscrotal cases. The incidence of complicating retention of the testes among 214 hypospadias is compared with the incidence among the general Danish population. This reveals an increased incidence of retention in all degrees of hypospadias.

### *Chapter 2*

After reviewing previous studies on the incidence of hypospadias the writer reports his own findings. Ninety cases occurred among 27 613 baby boys aged about 10 days. This is taken to represent the incidence among the total male population as there is no reason to believe that the mortality among hypospadias is particularly high. About three quarters of the cases were juxtaglandular about one eighth penile and about one eighth penoscrotal or perineoscrotal.

### *Chapter 3*

The views regarding the fertility of hypospadias advanced so far have been based mainly on theoretical considerations. In the present study the frequency of marriage among 77 patients over 20 years of age proved to accord with that among the general male population. The patients' sexual relations do not appear to differ essentially from normal once surgical correction of the severe forms of penile flexion has

been accomplished. The fertility of 47 married patients in relation to the severity of their defect proved normal in juxtaglandular — and perhaps also in penile — cases whereas in more severe cases it was reduced but not abolished.

#### *Chapter 4*

Previous genetic studies consist of case reports comprising more or less thoroughly investigated families and twin series — apart from Iamy's series of 10 pairs of twins. Therefore although indicated by various findings the hereditary nature of the lesion has not been proved so far. Exogenous factors must be presumed to play a part as Iamy reported discordance in three out of six pairs of monozygotic twins.

#### *Chapter 5*

To study the genetic aspect the writer collected a proband and a twin series. Out of 173 proband families 103 were examined, 43 partially examined while 27 had to be ruled out. The genitals of the male relatives were examined except in 48 % who refused to submit to the examination.

#### *Chapter 6*

The familial cases are presented in pedigrees and the solitary ones in tables. The number of males examined and not examined in each family is given. The study of the 12 pairs of twins is reported.

#### *Chapter 7*

The material is considered as a whole since there is familial occurrence in all degrees of the lesion — in an average of about 28 % — and marked intrafamilial variation in the severity. The defect is interpreted as an inherited lesion as the incidence was increased among the probands' relatives and as concordance was found more often in monozygotic than dizygotic twins.

The writer compares the degree of manifestation in the twin series with the degree of manifestation calculated on the basis of the actual findings and the number of cases expected among the close relatives at dominant and recessive heredity respectively. This calculation indicated recessive heredity with failing manifestation.

It cannot be ruled out that some instances are of purely exogenous origin.

Consanguinity occurred in three out of 124 patients' parents (2.4 %).

### Chapter 8

This chapter deals with Goldschmidt's intersexuality theory and certain views regarding the relation of hypospadias to this theory. If hypospadians are intersexes according to this theory, their genetic sex must be female. The writer, therefore, set out to study the sex distribution among the children and siblings of the hypospadians in the present series. According to the findings, hypospadians cannot be interpreted as female individuals. The distribution of a sex-linked recessive character — in this case colour blindness — among the patients and their parents also does not accord with the view that hypospadias is a form of intersexuality according to the theory of Goldschmidt.

The mothers' data regarding hormonal disturbances during pregnancy were studied. This gave no evidence to interpret hypospadias as a hormonal form of intersexuality. The age distribution among the mothers does not differ from that expected.

### Chapter 9

Perusal of 90 birth records and data regarding the pregnancy of 34 mothers afforded no reason to attach aetiological significance to foetal infections, defective nutrition, somatic or psychic traumas, intoxications or hæmorrhages during pregnancy.

Reporting the complicating malformations in the present series, the writer tries to relate them to the hypospadias.

In the five cases of discordant twins whose birth weight is known, the malformed twin was the smaller one. On the other hand the birth weight of hypospadians on the whole did not differ from the expected values.

### Chapter 10

Eugenics and operative indications are discussed. There is no indication for eugenic measures. There is no reason to advise hypospadians against having children. The possibility of improving the fertility, if reduced, must therefore be included in one's contemplations regarding the operative indications. In the author's opinion, there is no indication to operate in juxtaglandular cases.

## RESUME

### *Indledning*

Arbejdets formål er hovedsageligt at belyse hypospadiens ætiologi

### *Kapitel 1*

Ved en gennemgang af lidelsens morfologi påpeges, at der findes en jævn overgang mellem lette og svære grader. For det foreliggende arbejde er det mest praktiske en inddeling i juxtaglandære, penile, penoscrotale og perineale tilfælde. Differentialdiagnosen diskuteres på basis af egne tilfælde. Hyppigheden af komplicerende testisretention hos 274 hypospadipatienter sammenlignes med testisretentionens hyppighed i den danske befolkning. Herved findes forøget hyppighed af testisretention for alle hypospadigrader.

### *Kapitel 2*

Efter en kritisk gennemgang af tidligere undersøgelser over hypospadiens hyppighed, gøres rede for egne undersøgelser. Ved disse fandt man 90 tilfælde blandt 27 613 ca. 10 dage gamle drengebørn. Denne hyppighed henyttes som et udtryk for hyppigheden i den samlede mandlige befolkning, da hypospadipatienter næppe har nogen overdødelighed. Man finder, at ca.  $\frac{2}{3}$  af tilfældene er juxtaglandære, ca.  $\frac{1}{3}$  penile og ca.  $\frac{1}{4}$  penoscrotale og perineoscrotale.

### *Kapitel 3*

De tidligere anskuelser om hypospadipatienters fertilitet, der væsentligt er baseret på teoretiske betragtninger, omtales. I egne undersøgelser findes hyppigheden af ægteskaber for 77 patienter over 20 år at stemme overens med hyppigheden af ægteskaber i den mandlige befolkning. Patienternes seksuelle forhold synes ikke at afvige væsentligt fra det normale, når en sværere krumning af penis er operativt udrettet.

Og ved en vurdering af 47 gifte patienters fertilitet sammenholdt med deres misdannelses sværhed findes normal fertilitet for de juxtaglandære — og måske de penile — tilfælde, for de sværere nedsat, men ikke ophævet fertilitet

#### Kapitel 4

Da de tidligere undersøgelser over arveligheden består af kasuistiske meddelelser om mere eller mindre velundersøgte slægter og tvillingpar, bortset fra Lamy's tvillingmateriale på 10 par, er det ikke tidligere bevist, at hypospadi er arvelig, selvom forskellige forhold taler herfor. Exogene faktorer er formentlig af betydning, da Lamy fandt diskordans i 3 af de 6 eenæggede tvillingpar

#### Kapitel 5

Til arbejdets arvelighedsundersøgelse er indsamlet et proband- og et tvillingmateriale. Af 173 probandslægter er 103 undersøgte, 43 delvist undersøgte, medens 27 udgår. De mandlige slægtninges genitalia er undersøgte, dog har 4,8 % af de opsøgte slægtninge afslået en sådan undersøgelse.

#### Kapitel 6

De familiære tilfælde er illustreret ved slægtsskemaer og de solitære er opstillet i tabeller. Antallet af undersøgte og ikke undersøgte mandlige slægtninge er markeret i hver enkelt slægt. Undersøgelsen af de 12 tvillingpar er anført.

#### Kapitel 7

Materialet vurderes under et, da der findes familiær forekomst for alle grader af lidelsen — gennemsnitlig i ca. 28 % — og der forekommer en betydelig intrafamiliar variation i tilfældenes sværhed. Man anser lidelsen for arvelig, da den findes med forøget hyppighed blandt probandernes slægtninge, og eenæggede tvillingpar hyppigere end toæggede udviser konkordans.

Manifestationsgraden i tvillingmaterialet og manifestationsgraden, udregnet på basis af det fundne og det for henholdsvis dominant og recessiv arvegang forventede antal tilfælde i de nærmeste slægtningegrupper sammenlignes. Herved findes størst sandsynlighed for recessiv arvegang med svigtende manifestation.

Det kan ikke udelukkes at nogle tilfælde er rent exogent betingede. Indgifte fandtes hos 3 af 124 patienters forældre (2,4 %).

### Kapitel 8

Goldschmidts intersexualitets-teori og nogle anskuelser om hypospadiaens relation til denne omtales i 11 hypospadipatienter intersexer efter denne teori må deres genetiske køn være hunligt. I dette materiale har man derfor undersøgt kønsfordelingen blandt hypospadipatienternes børn og i deres søskendeflokke. Disse fordelinger tillader ikke at hypospadipatienter opfattes som hunlige individer. Fordelingen af en kønsbundet recessiv egenskab som farveblindhed blandt patienterne og deres forældre stemmer heller ikke overens med anskuelserne om hypospadi som en intersexualitetsform efter Goldschmidts teori.

Man har gennemgået oplysninger om mødrene med henblik på hormonale forstyrrelser. Der blev i dette materiale ikke fundet holdepunkter for at hypospadi kunne opfattes som en hormonal intersexualitetsform. Fordelingen af mødrenes alder afviger ikke fra den forventede.

### Kapitel 9

Ved en gennemgang af 90 fødejournaler og oplysninger om 34 mødres graviditet findes ingen holdepunkter for at føtale infektioner, ernæringsmangler, somatiske eller psykiske traumer, intoxicationer eller blødninger i svangerskabet er af ætiologisk betydning.

De komplicerende misdannelser i kødet materiale omtales, og man søger at sætte udviklingen af disse i relation til udviklingen af hypospadi.

Fødselsvægten var mindst hos den misdannede tvilling i de 5 af materialets tvillingepar med diskordans, hvor man havde oplysninger om fødselsvægten. Men 90 hypospadipatienters fødselsvægt afveg ikke fra det forventede.

### Kapitel 10

Arvehygiejne og operationsindikationer diskuteres. Der er ikke indikation for arvehygiejniske forholdsregler. Der er ingen grund til at fraråde hypospadipatienter at få børn. Muligheden af at bedre en evt. nedsat fertilitet må derfor inddrages i overvejelserne om operationsindikation. Man finder det ikke indiceret at operere de juxtaglandrørelse.

Og ved en vurdering af 47 giftes patienters fertilitet sammenholdt med deres misdannelses sværhed findes normal fertilitet for de juxtaglandulae — og måske de penile — tilfælde for de sværere nedsat men ikke ophævet fertilitet

### Kapitel 4

Da de tidligere undersøgelser over arveligheden består af kazuistiske meddelelser om mere eller mindre velundersøgte slægter og tvillingpar bortset fra Lamy's tvillingmateriale på 10 par er det ikke tidligere blevet vist at hypospadi er arvelig selvom forskellige forhold taler herfor. Exogene faktorer er formentlig af betydning da Lamy fandt diskordans i 3 af de 8 eenæggede tvillingpar.

### Kapitel 5

Til arbejdets arvelighedsundersøgelser er indsamlet et proband og et tvillingmateriale. Af 173 probandsløgter er 103 undersøgte 43 delvist undersøgte medens 27 udgår. De mandlige slægtinges genitalia er undersøgte dog har 48 % af de opsøgte slægtinge afslået en sådan undersøgelse.

### Kapitel 6

De familiære tilfælde er illustreret ved slægtskemaer og de solitære er opstillet i tabeller. Antallet af undersøgte og ikke undersøgte mandlige slægtinge er markeret i hver enkelt slægt. Undersøgelsen af de 12 tvillingpar er anført.

### Kapitel 7

Materialet vurderes under et da der findes familier forekomst for alle grader af lidelsen — gennemsnitlig i ca. 28 % — og der forekommer en betydelig intrafamiliær variation i tilfældenes sværhed. Man anser lidelsen for arvelig da den findes med forøget hyppighed blandt probandernes slægtinge og eenæggede tvillingpar hyppigere end toæggede udviser konkordans.

Manifestationsgraden i tvillingmaterialet og manifestationsgraden udregnet på basis af det fundne og det for henholdsvis dominant og recessiv arvegang forventede antal tilfælde i de nærmeste slægtingegrupper sammenlignes. Herved findes størst sandsynlighed for recessiv arvegang med svigtende manifestation.

Det kan ikke udelukkes at nogle tilfælde er rent exogent betingede. Indgifte fandtes hos 3 af 124 patienters forældre (2.4 %).

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*Man har gennemgået oplysninger om mødrene med henblik på hormonale forstyrrelser. Der blev i dette materiale ikke fundet holddepunkter for, at hypospadi kunne opfattes som en hormonal intersexualitetsform. Fordelingen af mødrene's alder afviger ikke fra den forventede.*

### Kapitel 9

*Ved en gennemgang af 90 fødejournaler og oplysninger om 34 mødres graviditet findes ingen holddepunkter for, at totale infektioner, ernæringsmangler, somatiske eller psykiske traumer, intoxicationer eller blodninger i svangerskabet er af aetiologisk betydning.*

*De komplicerende misdannelser i eget materiale omtales, og man søger at sætte udviklingen af disse i relation til udviklingen af hypospadi.*

*Fødselsvægten var mindst hos den misdannede tvilling i de 5 af materialets tvillingpar med diskordans, hvor man havde oplysninger om fødselsvægten. Men 90 hypospadipatienters fødselsvægt afveg ikke fra det forventede.*

### Kapitel 10

*Arvhygiejne og operationsindikationer diskuteres. Der er ikke indikation for arvhygiejniske forholdsregler. Der er ingen grund til at fraråde hypospadipatienter at få børn. Muligheden af at bedre en evt. nedsat fertilitet må derfor inddrages i overvejelserne om operationsindikation. Man finder det ikke indiceret at operere de juxtaglandre tilfælde.*



## REFERENCES

(Abbreviations in conformity with the Quarterly Cumulative Index Medicus  
The figures in brackets indicate the pages in the present work on which the  
respective author has been cited)

- 1) *Albaugh C H* Congenital anomalies following maternal rubella in early weeks of pregnancy *J A M A* 129 719—723 1945 (76)
- 2) *Irey Leslie Brainerd* Developmental anatomy Philadelphia and London W W Saunders Company 1942 Pp 612 (79)
- 3) *Bardram Mogens & Poul Brændstrup* Maternal rubella during pregnancy as a cause of congenital cataract and other congenital malformations *Acta ophth* 25 353—367, 1947 (76)
- 4) *Barragan* Critique des différentes méthodes opératoires de l'hypospadias *Rev de chir Paris* 43 887—888 1911 (23 27)
- 5) *Bendixen H C* Littery occurrence of anophthalmia or microphthalmia together with other malformations in swine — Presumably due to vitamin A deficiency of the maternal diet in the first stage of pregnancy and preceding period *Acta path et microbiol Scandinav suppl* 54 161 1944 (76)
- 6) *Berblinger W* Männlicher Geschlechtsapparat In *Pathologische Anatomie* Herausgeben von Ludwig Aschoff Achte Auflage Bd II Jena Verlag von Gustav Fischer 1936 P 494 (69)
- 7) *Bjerre Hans* Kliniske undersøgelser over ingvinalkryptorchismen hos mennesket Copenhagen Ejnar Munksgaard 1935 Pp 274 P 50 Diss (22)
- 8) *Brendler Herbert* A new method for the construction of a glandular urethra in hypospadias repair *J Urol* 59 1164—1168 1948 (83)
- 9) *Broster L R* The adrenals in sex *Practitioner* 158 307—314 1947 (73)
- 10) *Bucht E C* Über die Abhängigkeit der Missbildungen von Gebäralter *Arch d Julius Klaus Stiftg f Vererbungsforschg* 25 61—65 1950 (25 74)
- 11) *Bullock W* Hereditary malformations of the genital organs Hermaphroditism In *Treasury of human inheritance* Part III London & Edinburgh Cambridge University Press 1909 P 50—61 (40 41)
- 12) *Camerer J W* Diskordantes Vorkommen einer Hypospadias bei einem eineiigen Zwillingpaar *Erbartz* 5 105 1938 (42)
- 13) *Campbell Meredith F* Stenosis of the external urethral meatus *J Urol* 50 740—746 1943 (25)

- 14) *Comptell Meredith F.* Hypospadias When to operate (Editorial) *Am J Surg New Series* 74 795—796 1947 (23)
- 15) *Carroll William A.* Malignancy in cryptorchidism *J Urol* 61 396—401 1949 (26)
- 16) *Cheyne W. Watson & F. F. Burghard.* A manual of surgical treatment New York Bombay and Calcutta Longmans Green & Company, 1913 Pp 618 P 323—332 (13)
- 17) *Dantchakoff Vera.* L'hormone mâle à la base de l'édification du pénis et de ses malformations chez les mammifères *Compt rend Soc de biol* 127 674 677 1938 (73)
- 18) *Diaz J. Thomas.* Pseudohermaphroditism *Am J Dis Child* 60 67—72 1943 (16)
- 19) *Dodds Lortimer.* Maternal rubella as a cause of congenital defects in infancy *Acta paediat* 36 197—202 1948 (77)
- 20) *Fugberg Harold.* Testis endokrine funktion ved kryptorchisme Copenhagen Ejnar Munksgaard 1948 Pp 216 P 72 Diss (20 21)
- 21) *Fogh Andersen Pont.* Hypospadi Ugesk f Læger 110 231—236 1903 (82)
- 22) *Franzenheim Paul.* Klinik der Missbildungen der Harn und Geschlechtsorgane In *Handbuch der Urologie* Herausgeben von A. v. Lichtenberg F. Voelcker und H. Wütholz Bd III Berlin Julius Springer, 1928 P 282—303 (11 12 13)
- 23) *Fraser F. Clarke & T. D. Fainstat.* Production of congenital defects in the offspring of pregnant mice treated with cortisone *Pediatrics* 8 527—533 1951 (76)
- 24) *Fruhmann P. & H. Sternberg.* Untersuchungen an Kryptorchiden und Hypospadien *Arch f klin Chir* 160 633—673 1930 (20)
- 25) *Gates Reginald Ruggles.* Human genetics Vol 1—2 New York The Macmillan Company 1946 Pp 1518 P 852 (46)
- 26) *Goldschmidt Richard.* Ueber die Vererbung der sekundären Geschlechtscharaktere München med Wchnschr 58 2642—2643 1911 (68)
- 27) *Goldschmidt Richard.* Vorläufige Mitteilung über Versuche zur Vererbung und Bestimmung des Geschlechts *Biol Centralbl* 30 565—570 1915 (68)
- 28) *Goldschmidt Richard.* Die sexuellen Zwischenstufen Berlin Verlag von Julius Springer 1931 Pp 528 (68 69)
- 29) *Goldschmidt Richard.* Ismantria *Bibliographia Genetica* XI 1933 Pp 186 (68)
- 30) *Goldstein Albert F.* Congenital anomalies of the genitourinary tract In *A textbook of surgery by American authors* Edited by Frederick Christopher Philadelphia & London W B Saunders 1946 Pp 1548 P 1229 (11 12 13)
- 31) *Greene R. R.* Hormonal factors in sex inversion The effects of sex hormones on embryonic sexual structures of the rat *Biol Symp* 11 105—123 1942 (73)
- 32) *Greene R. R.* Embryology of sexual structure and hermaphroditism *J Clin Endocrinol* 4 335—348 1944 (73)
- 33) *Grunfelder H. & W. Tusch.* Der Zeitpunkt einer embryonalen Entwicklungsstörung als ursächliche Moment kongenitaler Anomalien *Ann Paediat* 173 388—404 1949 (77)

- 34) *Gorf Grethe* Om forbyggende helbredsundersøgelser af børn i den forskolepligtige alder Ugesk I Læger 113 794—803 1951 (21 24)
- 35) *Hansen Torben Svend* Fertiliteten ved operativt behandlet og ubehandlet kryptoichisme Copenhagen Ejnar Munksgaard 1945 Pp 190 Diss (19 21)
- 36) *Higgins Charles C* Hypospadias Cleveland Clin Quart 14 126—127 1947 (27)
- 37) *Hinman Frank* Principles and practice of urology Philadelphia & London W B Saunders Company 1937 Pp 1111 P 414—418 (12 13)
- 38) *Hooks Charles I* Clinical aspects of intersexuality J Urol 62 528—534 1949 (15)
- 39) *Howard Frederick S* Hypospadias with enlargement of the prostatic utricle Surg Gynec & Obst 86 307—316 1948 (12)
- 40) *Ingalls Theodore H Francis J Curley & Richard Prindle* Anoxia as a cause of fetal death and congenital defects Am J Dis Child 80 34—45 1950 (76 77)
- 41) *Ipsen jr John & Harald Økkels* Om atresia osotica congenita med osotagotrachealfistel samt bemærkninger om synkronier ved misdannelsens opståen Hospitalstid 75 1083—1091 1113—1118 1932 (77)
- 42) *Ishihara S* Tests for colour blindness 7th edition Tokyo Osaka Kyoto Kanehara & Co 1936 (72)
- 43) *Jacobsen I M* Personal communication 1949 (25)
- 44) *Jeanbrau Emile* Appareil genital de l'homme Dans Précis de pathologie chirurgicale Tome V Paris Masson et Cie 1937 P 581—588 (11 13)
- 45) *Johnson Franklin P* Surgery of the urethra and penis In Nelson new loose leaf surgery Vol VI New York Toronto London Edinburgh Paris Melbourne Thomas Nelson & Sons 1929 P 70 (11 12 13)
- 46) *Kaufmann C* Verletzungen und Krankheiten der männlichen Harnrohre und des Penis In Deutsche Chirurgie Herausgeben von Biliroth und Iuecke Heft 50 a Stuttgart Verlag von Ferdinand Enke 1886 P 18—39 (11 12 13)
- 47) *Keizer D P R* Hallux valgus congenitus avec hypospadias penis Paris med 40 566 1950 (76)
- 48) *Kemp Tage* Erbbiologie und Erhpathologie des Geschlechtsapparates In Handbuch der Erbbiologie des Menschen Band IV/2 Berlin Verlag von Julius Springer 1940 P 939—941 (40)
- 49) *Kemp Tage* Statistiske metoder i medicin og biologi Copenhagen Ejnar Munksgaard 1942 Pp 172 (22 24 64 65)
- 50) *Kemp Tage* Arvelighedslære Copenhagen Ejnar Munksgaard 1943 Pp 285 (66)
- 51) *Koller Stegfried* Methodik der menschlichen Erbforschung In Handbuch der Erbbiologie des Menschen Band II Berlin Verlag von Julius Springer 1940 P 264 (72)
- 52) *Kovacs Zoltan* Über Hermaphroditismus Brun's Beitr z klin Chir 173 424—438 1942 (15)
- 53) *Lamy Maurice* Lecture read at the University Institute of Human Genetics Copenhagen April 18 1952 (42 65)
- 54) *Langstein L* Erkrankungen des Urogenitalsystems In Pfandlner und

- Schlossmann Handbuch der Kinderheilkunde Band IV Leipzig Verlag von J. C. W. Vogel 1910 P 122 (23)*
- 55) *Lehmann Wolfgang* Hypospadie bei einem einseitigen Zwillingspaar *Erhardt* 3 147 1936 (42)
  - 56) *Lesser Edmund* Beitrag zur Vererbung der Hypospadie *Virchows Arch f. path. Anat.* 116 537 539 1889 (41)
  - 57) *Lingard Alfred* The hereditary transmission of hypospadias and its transmission by indirect albinism *Lancet* I 703 1881 (40)
  - 58) *Loughran I W* Observations on hypospadias including the late results of Ombredanne's urethroplastic operation *Brit J Plast Surg* 1 147—158 1948 (13 40)
  - 59) *Murx Gunther* Zur Chirurgie einiger körperlicher Missbildungen und ihre Bedeutung für das Gesetz zur Verhütung erbkranken Nachwuchses *Arch f. klin. Chir.* 192 645 656 1933 (29)
  - 60) *Mayo C H* Hypospadias *J. A. M. A.* 36 1157 1162 1901 (29)
  - 61) *McGrea F. d. Arcy* Diseases of the urethra and penis *Bristol John Wright & Sons Ltd London Simpkin Marshall Ltd 1940 Pp 306 P 45—65 (11 12 13 23)*
  - 62) *Moore Carl R* Sex endocrines in development and prepubertal life *J Clin Endocrinol* 4 135 141 1944 (73)
  - 63) *Mosekotte Ludwig* Hermaphroditismus und andere geschlechtliche Zwischenstufen beim Menschen *Ergebn d. allg. Path. u. path. Anat.* 31 236—444 1936 (69)
  - 64) *Mowry I F* Some genital defects noted in examination of 10 000 limited service men at camp Syracuse *Urol. & Cutan. Rev.* 23 529—530 1919 (23 27 29)
  - 65) *Nachtshelm Hans* Ichnokopien Lecture read at the University Hospital Copenhagen in the autumn of 1951 (76)
  - 66) *Nahouri Antoine* One stage operation for correction of mild hypospadias *J Urol* 59 74 77 1947 (81)
  - 67) *Neubauer Franz Ludwig von* Hermaphroditismus beim Menschen *Leipzig Verlag von Dr. Werner Klinkhardt 1908 Pp 748 (12 15 27 29 40)*
  - 68) *Ombredanne J* Précis clinique et opératoire de chirurgie infantile *Paris Masson et Cie 1932 Pp 1480 P 859—873 (11 12 13 29 40)*
  - 69) *Popper Rudolf* Die Entwicklung des Praeputium clitoridis mit Bemerkungen über die Homologisierung von Praeputium penis und Praeputium clitoridis und über das praeputium der Hypospadien *Ztschr. f. Anat. u. Entwicklungsgesch.* 107 378—387 1937 (69)
  - 70) *Prendergast John J* Congenital cataract and other anomalies following rubella in mother during pregnancy *Arch. opht.* 35 39—41 1946 (71)
  - 71) *Rennes M* Observations médicales sur quelques maladies rares ou peu connues, et particulièrement sur les affections des organes génitaux *Archives générales de Médecine* 27 17 1831 (23 27)
  - 72) *Rhodes Adrian* Pseudohermaphroditism in twins *Arch. Pediatr.* 60 529—536 1943 (42)
  - 73) *Sand Knud* Sexualabnormitäten und Namenwechsel (Aus dem Verhandlungsbericht des I. Internationalen Kongresses für gerichtliche und soziale Medizin Bonn u. Rh. 1938) *Med. fakultet fra Universitetets rets medicinske Institut* 10 1940 (15)

- 74) *Schaefer Arthur I & John Irbes* Hypospadias *Am J Surg* 80 183—191 1950 (13 40)
- 75) *Schmidt Clinton K* Surgical procedure for correction of hypospadias *J Urol* 40 239—247 1938 (13)
- 76) *Schneider P* Die Missbildungen der männlichen Geschlechtsorgane. In *Handbuch der Urologie* Herausgeben von A v Lichtenberg F Voelcker und H Wildbolz Band III Berlin Julius Springer 1928 P 145—153 (11 13 23 27)
- 77) *Schurer F von* Zum Problem der Fruchtbarkeit des Mannes *Wien klin Wchnschr* 52 403—407 1939 (23 29)
- 78) *Stevens Roderich* Anomalien am Penis Ihre Beziehungen zur Hypospadias und ihre Deutung *Deutsche Ztschr f Chir* 199 286—305 1920 (12)
- 79) *Sjaulding M H* The development of the external genitalia in the human embryo *Carnegie Contribution to Embryology* 13 69 87 1921 (77)
- 80) *Statistique du Danemark* Annuaire statistique Copenhagen Gylden bol ske Boghandel Nordisk Forlag 1945 (30 78)
- 81) *Steiner F* Zur Erbllichkeit der Hypospadias Munchen med Wchnschr 83 1271 1936 (42)
- 82) *Sorensen Hans Rahbek* Behandlung af hypospadias *Ombredannede Ugeskr f Leger* 110 207—208 1948 (29)
- 83) *Thompson A K* Hypospadias Its effects symptoms and treatment *Lancet* 233 429—432 1937 (12 13)
- 84) *Verschuer Otmar von* Anomalien der Korperform In *Menschliche Erblehre und Rassenhygiene* Band I/2 Munchen Berlin J P Lehmanns Verlag 1940 P 150 (42)
- 85) *Waelel Georg H M* Über die Erbllichkeitverhältnisse der verschiedenen Arten von angeborener Rotgrünblindheit *Ztschr f induktive Abstammungs u Vererbungslehre* 44 279—333 1927 (72)
- 86) *Wagenen G van & James B Hamilton* The experimental production of pseudohermaphroditism in the monkey *Essays in biology in honor of Herbert M Evans* Berkely & Los Angeles University of California Press 1943 P 583—607 (73)
- 87) *Warkany Josef* Congenital malformations induced in rats by maternal nutritional deficiency *Acta paediat* 36 293—299 1948 (76)
- 88) *Wehner Ernst* Die Chirurgie der Harnrohre In *Die Chirurgie* Herausgeben von Martin Kirschner und Otto Nordmann Band VII Berlin & Wien Urban & Schwarzenberg 1942 P 718 (13)
- 89) *Weit Wilhelm* Die Vererbung innerer Krankheiten In *Menschliche Erblehre und Rassenhygiene* Band I/2 Munchen Berlin J P Lehmanns Verlag 1940 P 239 (40)
- 90) *Young Hugh Hampton* Genital abnormalities and related diseases London Balliere Tindall & Cox 1937 Pp XXXVIII + 650 P 411—439 (13)





